Group B streptococcal disease: screening and treatment in pregnancy

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Intermittent, asymptomatic colonisation of the vagina and rectum with group B streptococci is common in pregnancy. Vertical transmission of the bacterium from mother to fetus may lead to neonatal sepsis, characterised by pneumonia, meningitis and death in the most severely affected babies. Intrapartum prophylaxis with penicillin reduces the burden of disease when given to women with risk factors for the development of group B streptococcal sepsis such as preterm labour, prolonged rupture of the membranes or maternal pyrexia in labour. Some professionals advocate the universal screening of all pregnant women for group B streptococci near term and the administration of intrapartum antibiotic prophylaxis to all women testing swab-positive. This article summarises the salient features of group B streptococcal disease and explores the rationale behind the use of intrapartum antibiotics for the prevention of neonatal infection.

Introduction

Maternal colonisation

Group B streptococci (GBS) are facultatively anaerobic, Gram-positive bacteria. They colonise the rectum or vagina in approximately 28% of the pregnant population, although their presence in the genital tract tends to be transient or intermittent rather than chronic. Carriage rates vary between different countries and ethnic groups, with rates as high as 41% being reported in African American populations but rates as low as 12% being reported on the Indian subcontinent.

For most women, GBS colonises the lower vagina or rectum as an asymptomatic commensal organism. Occasionally, however, clinical evidence of maternal infection with GBS arises in the form of urinary tract infection, chorioamnionitis or postpartum endometritis. Maternal symptoms tend to be mild, although systemic sepsis and meningitis have been described.

Clinical features of perinatal infection

When GBS colonisation occurs during pregnancy, the fetus may be exposed in utero as the bacterium ascends or as the fetus descends through the genital tract. This process is facilitated by the ability of GBS to adhere to chorionic membranes, although infection is more likely following prolonged membrane rupture. Congenital pneumonia resulting in fetal demise before or during labour is well documented. More commonly, however, clinical evidence of sepsis does not become apparent until birth. Early-onset group B streptococcal sepsis (EOGBSS) is defined as presentation within the first 72 hours of life, the majority of babies developing signs of infection within a few hours of birth. Most babies with EOGBSS present with nonspecific signs of systemic infection including poor feeding, lethargy and temperature instability. Pneumonic and meningitic presentations are also common, while rarer complications such as osteomyelitis and septic arthritis are occasionally encountered. All babies developing EOGBSS are at risk of death or long-term neurodevelopmental impairment and this is especially so for those who develop meningitis (Figure 1).

GBS sepsis has been recognised as an important cause of neonatal morbidity for over 30 years and is now known to be the most common serious neonatal infection in the developed world. The current UK prevalence of EOGBSS confirmed by
bacteriological culture is approximately 0.58 cases per 1000 live births, although some authors believe the true prevalence to be significantly higher at around 3.6 per cases 1000 live births. Case fatality rates have improved in recent years, with advances in neonatal care, but still stand at between 4% and 10%, with higher rates recognised for babies born prematurely. Seminal studies in the USA in the mid-1980s were able to show that the number of babies developing EOGBSS could be reduced dramatically by administering intrapartum antibiotic prophylaxis to women, thereby decreasing bacterial transmission to the fetus rather than treating fetal infection itself. There are essentially two strategies for the prevention of EOGBSS that have been developed around this idea. In the ‘risk-based’ approach, intrapartum antibiotic prophylaxis is given to any woman whose clinical history suggests that her baby is at high risk of developing EOGBSS, such as a woman with prolonged membrane rupture. In the ‘universal prenatal screening’ approach, intrapartum antibiotic prophylaxis is given to all women known to be colonised with GBS, even in the absence of clinically based risk factors.

The risk-based strategy

Risk factors for EOGBSS are well established and have been confirmed in case–control studies (Table 1). In addition, babies born to women with a previously affected child are also at an increased risk. The risk-based strategy requires women with any one of these risk factors to be given intrapartum antibiotic prophylaxis. The strategy also allows for women with a positive urine culture and women with a fortuitous finding of GBS on any vaginal or cervical swab taken during the index pregnancy to be treated. If these criteria were strictly applied to the UK population, at least 16% of women would receive antibiotics in labour. It is estimated that approximately 625 women with one or more of these risk factors would need to be treated to prevent one case of EOGBSS, and one neonatal death would be prevented for every 5882 women treated.

Although the number of women requiring treatment in this scheme appears high, in 1996 the US Centers for Disease Control and Prevention (CDC) published guidelines accepting the risk-based approach as a viable alternative for the prevention of EOGBSS. The principle that a calculation of risk should be used to inform maternal choice was later endorsed by the Public Health Laboratory Service (PHLS) GBS Working Group in the UK and forms the basis of advice given in the present RCOG Guideline. Subsequent experience in the USA confirmed that, when rigorously applied, intrapartum antibiotic prophylaxis given to women with risk factors for EOGBSS could deliver a clear reduction in neonatal morbidity and mortality. Reflecting this, implementation of the risk-based treatment strategy measurably reduced high-dependency neonatal special care cot occupancy in US states implementing the strategy. Given the high cost...
of neonatal intensive care and supportive treatments such as extracorporeal membrane oxygen, a similar experience in the UK might effectively make the exercise cost neutral to the NHS.

While this approach has many advocates, 30–40% of babies with EOGBSS are born to women with no identifiable risk factors. Even rigorous application of the risk-based strategy cannot, therefore, reduce the incidence of EOGBS by more than 60–70%. Experience from the USA suggests that this is true in practice, leading the CDC to publish guidelines backing the potentially more effective alternative strategy of universal prenatal screening.17

### Universal prenatal screening

The 2002 CDC guidelines recommended bacteriological screening for all pregnant women and the use of intrapartum antibiotic prophylaxis for all screen-positive women, regardless of the presence or absence of other risk factors for EOGBSS. To achieve this, low vaginal and endonal swabs must be taken at 35–37 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 intrapartum antibiotic prophylaxis, 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 instruction, most pregnant women can take their own swabs, improving the acceptability of the procedure without affecting its sensitivity.18 A sample of urine should also be analysed in the third trimester, since GBS bacteriuria is associated with exposure of the fetus to a high bacterial load.19

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,20 the assay sensitivity can be increased dramatically.

Some babies exposed to GBS will develop early-onset disease even after optimal antibiotic prophylaxis, particularly when infection has arisen in utero.21 Nevertheless, US states employing the screening strategy have reported a reduction in rates of EOGBSS of up to 86%, a decline that is significantly better than that found in states following the risk-based strategy.17

In the UK, implementation of a universal prenatal screening policy would impact significantly upon the provision of antenatal care. 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. The screening system would also have to comply with the NICE guidelines on the provision of routine antenatal care.22 Access to written information and personal, professional advice would be needed before swabs were obtained, when results were available and prior to instituting antibiotic prophylaxis. While these requirements could be met in the course of present antenatal care arrangements for most women, some additional time allocation would inevitably be required to fulfil the counselling obligations attendant to the screening programme.

Although the National Screening Committee in the UK is currently considering adoption of the universal screening approach, this is unlikely to be their favoured option because it would almost certainly lead to the treatment of more women with intrapartum antibiotic prophylaxis than would adoption of the risk-based approach, with up to 30% being offered antibiotics in labour.23 The finding of a positive swab would also impact upon the woman’s care in labour in a wider sense, influencing the woman’s decision regarding place of confinement and possibly colouring clinicians’ views when choosing management options in labour. Furthermore, the cost implications of universal prenatal screening would be significant, even though a reduction in usage of high-dependency neonatal care might be expected to

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### 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>
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<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 the membranes</td>
<td>25.8</td>
<td>10.2–64.8</td>
</tr>
<tr>
<td>Rupture prolonged rupture of the membranes &gt;18 hours</td>
<td>30.3</td>
<td>6.3–144.5</td>
</tr>
<tr>
<td>Intrapartum 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</td>
<td>Unquantified</td>
</tr>
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offset these costs to some degree. Perhaps, more pertinently, the balance may lie between the inconvenience to the mother and to the health service of implementing a screening programme, set against achieving the maximum possible reduction in neonatal morbidity and mortality.

Combining universal prenatal screening and the risk-based strategy

The Canadian Task Force on Preventative Health Care has shown that by adopting a universal screening strategy but then only offering intrapartum antibiotic prophylaxis to women who test swab-positive and who have additional risk factors for EOGBSS, the number of women treated with penicillin in labour can be reduced to as little as 3.4%. Although this approach is likely to cause less morbidity in labouring women by reducing antibiotic usage, it retains the financial and organisational obstacles inherent in implementing a universal antenatal screening programme and has the potential to reduce the incidence of EOGBSS by only a little over 50%. Because of these limitations, the approach is rarely encountered in UK or US practice.

Chemoprophylaxis and therapy

Intrapartum antibiotic prophylaxis

Several studies have confirmed the efficacy of intrapartum antibiotic prophylaxis for EOGBSS prevention, with most concluding that the use of antibiotics significantly reduces the rate of neonatal colonisation and sepsis. To be effective, it may be necessary for drug administration to commence 4 or more hours before delivery, since efficacy increases with both the length of time the fetus has been exposed to antibiotics in labour and the number of doses administered. This 4-hour rule should not be adhered to dogmatically, since clear evidence defining the minimum necessary time exposure to intrapartum antibiotic prophylaxis to achieve neonatal benefit is lacking.

To date, there has been no reported resistance of GBS to either penicillin or ampicillin in vivo and virtually no resistance in vitro. Since ampicillin has a relatively broad spectrum of antimicrobial activity, its widespread use has the potential to select for resistant organisms. Because of this, penicillin remains the drug of choice for intrapartum antibiotic prophylaxis, given at an intravenous dose of 3 g (5 MU) initially then 1.5 g (2.5 MU) 4-hourly until delivery.

As much as 10% of the UK population claims to be allergic to penicillin. Although true allergic reactions probably occur in less than 1%, anaphylaxis has been reported in women receiving intrapartum antibiotic prophylaxis for GBS and might be expected to arise in 1/100 000 women treated. The RCOG estimates that, if a universal screening policy were adopted leading to the administration of intrapartum antibiotic prophylaxis to 30% of parturients, two anaphylaxis-related maternal deaths could be expected annually in the UK. In the search for a suitable alternative antibiotic, up to 25% of GBS isolates have been found to be resistant to erythromycin, which also fails to achieve bactericidal levels in the amniotic fluid. Up to 15% are resistant to clindamycin, the currently recommended second-line drug in the UK. First-generation cephalosporins such as cefazolin may be more effective and have the advantage of achieving high intra-amniotic concentrations while retaining a relatively narrow spectrum of antimicrobial activity.

In theory, the widespread use of intrapartum antibiotic prophylaxis could lead to an increase in the incidence of early-onset non-GBS sepsis in neonates, negating any beneficial effect. Clinicians might also expect to encounter an increase in the prevalence of drug-resistant bacteria causing disease. In reality, these phenomena have rarely been observed and some centres following CDC guidelines have actually recorded a fall in the incidence of non-GBS sepsis. To preserve this advantage, however, the use of antibiotics with a broad spectrum of activity should be reserved for women with true penicillin allergy and close surveillance should be kept of the range of bacteria causing neonatal disease.

Treating the neonate

Combining infant antimicrobial prophylaxis (100 mg/kg intravenous penicillin given daily in two divided doses) with intrapartum antibiotic prophylaxis reduces the rate of EOGBSS in both term and preterm infants when compared with a strategy of no intervention but such routine neonatal prophylaxis has not gained wide support and its benefits remain uncertain. At present, the PHLS, RCOG and CDC recommend that, in general, whether concern arises because of the presence of maternal risk factors or maternal swab results, babies who have received intrapartum antibiotic prophylaxis before birth require heightened observation alone for 12–48 hours after delivery, with intravenous penicillin reserved for babies developing signs of disease. As exceptions to this rule, penicillin should also be considered for babies who are otherwise well but who have a combination of
risk factors such as maternal GBS bacteriuria in the presence of prolonged membrane rupture. Most paediatricians also treat babies born to mothers with unequivocal features of chorioamnionitis, babies with twin siblings affected by EOGBSS and babies with siblings who have had previously confirmed EOGBSS.

Obstetric issues

The risk of fetal infection in women with intact membranes who are not in labour is low. Because of this, antibiotic cover for GBS need not be administered routinely to women undergoing an elective caesarean section, even in the presence of positive swabs. A dilemma may arise when, for example, a woman who is swab positive or has EOGBSS risk factors and who is due to be delivered by caesarean section presents with rupture of the membranes or in labour. In these circumstances, GBS cover may be given, accepting that delivery is likely to take place below the theoretical 4-hour prophylaxis threshold. Delaying delivery to achieve this threshold would be illogical, since fetal bacterial exposure increases with time. Standard obstetric practice dictates that some women with positive GBS swabs or risk factors for neonatal sepsis will undergo one of a number of common obstetric interventions during the course of pregnancy and labour. For example, induction of labour is as likely in this group of women as in the general population. There is no present evidence to suggest that antenatal vaginal examination, membrane sweeping or insertion of prostaglandin pessaries for labour induction increase the rate of transmission of GBS from the mother to the fetus. In labour, although neonatal infection rates increase in association with the frequency of vaginal examinations and the placement of fetal scalp electrodes, cause and effect have not been proven in these circumstances. Furthermore, there are few data available specifically relating GBS sepsis to these intrapartum procedures. There is, therefore, no clear evidence to suggest that women whose babies are at risk of EOGBSS should receive anything other than normal obstetric or midwifery care in labour in addition to antibiotic prophylaxis.

Issues relating to infants born prematurely

Approximately 6% of women give birth after spontaneous labour before 37 weeks of gestation and, of these, one-third give birth before 32 weeks. Premature babies are at particularly high risk of developing EOGBSS and they are also more likely to die or develop long-term sequelae as a result. The CDC recommends administration of intrapartum antibiotic prophylaxis to all women who seem likely to give birth because of preterm labour, regardless of the presence of membrane rupture, while the PHLS and the RCOG concur that intrapartum antibiotic prophylaxis should be considered in this group. When tocolytics are used in an attempt to arrest labour, low vaginal and rectal swabs should be taken to determine the woman’s colonisation status, although reliable results may not be available in time to influence the use of antibiotic prophylaxis. After delivery, continued treatment with penicillin is essential for babies showing signs of infection. In practice, signs of infection are frequently non-specific and it is also impossible readily to distinguish surfactant-deficient lung disease from congenital pneumonia, so it is common for preterm babies to receive antibiotics immediately after delivery.

Future perspectives

Rapid detection of GBS

Because of the transient or intermittent pattern of maternal colonisation normally encountered, an intrapartum assay for GBS could hold a significant advantage over an earlier screening test by more accurately reflecting the colonisation status of a woman in labour. For this, an assay would be required that could provide a result rapidly, that was highly sensitive to the presence of GBS and that was sufficiently specific to give a low false-positive result rate. Such a test would also allow the accurate assessment of women presenting with threatened preterm labour and preterm rupture of the membranes.

A number of GBS rapid detection kits are commercially available but, for many, their sensitivity is too low to allow effective intervention based on their results. A new polymerase chain reaction assay has been studied, which is sensitive to the presence of GBS in 97% of cases and claims 100% specificity. Furthermore, assay results are available within 45 minutes. The assay is not, however, currently commercially available so a true analysis of benefit remains to be determined.

Immunisation

Maternal immunisation against GBS prior to or during pregnancy has the potential to prevent fetal colonisation in utero, thereby eliminating GBS-mediated stillbirth in addition to EOGBSS. It could also impact significantly on late-onset disease firstly by reducing vertical
transmission of the bacterium and secondly by providing the neonate with passive immunity against infection acquired ex utero. At least eight different GBS serotypes exist, based upon the specific structure of the capsular polysaccharide and embedded proteins. Although only three or four serotypes are responsible for the majority of disease, a vaccine would nevertheless have to be multivalent to be effective. Current phase one and two clinical trials have generally investigated the use of monovalent vaccines, with limited potential for widespread disease prevention.\(^\text{34}\)

**Conclusions**

In order to meet the challenge of reducing morbidity and mortality caused by group B streptococcal disease after birth, the RCOG has proposed that a woman should be offered intrapartum antibiotic prophylaxis based upon maternal risk factor assessment.\(^\text{32}\) This contrasts with the current US CDC strategy based upon the use of universal prenatal screening. It is likely that the former policy will be cheaper to implement, easier to administer and less likely to impact adversely upon a woman’s care in labour, while the latter would possibly deliver greater reductions in neonatal disease. In the future, rapid assays for maternal GBS colonisation may be available for use in labour while vaccination against GBS represents the greatest hope of reducing the burden of neonatal and maternal disease. While GBS remains the most prevalent organism causing early-onset infections, it should be remembered that more than 50% of early-onset infections are caused by non-GBS organisms,\(^\text{35}\) so the eradication of EOGBS should not be seen as the endpoint in combating neonatal sepsis.

**References**

13. Heath P. Personal communication.