Early-onset neonatal group B streptococcal infection in London: 1990–1999

Albert J. Mifsud, a Androulla Efstratiou, b André Charlett, c A. Christine McCartney b

on behalf of the Health Protection Agency Group B Streptococcus Working Group

Objective To identify the incidence of early-onset group B streptococcal infection and to describe the antecedent maternal risk factors, in order to provide data to inform the design of interventional strategies that could be introduced in the UK to reduce the burden of this infection.

Design A retrospective study with review of case notes of mothers and babies.

Setting Seven maternity units in London during 1990–1999.

Population All cases of proven early-onset neonatal group B streptococcal infection.

Methods Identification of presence of risk factors that could be used to select women for the offer of intrapartum antibiotic prophylaxis.

Main outcome measures Incidence and case-fatality rate of invasive early-onset group B infection.

Results One hundred and forty cases were identified among a birth cohort of 198,388 live births, an incidence of 0.71 per 1000 live births. Twenty-two babies died, a case-fatality rate of 15.6% or 1.1 per 100,000 live births. Women of black ethnic origin, and those who had had a previously affected infant, multiple pregnancy, preterm delivery, prolonged rupture of membranes or intrapartum fever all had a significantly increased risk of delivering an infected infant.

Conclusions These data suggest that the incidence of early-onset group B streptococcal infection in these London centres is sufficiently high to warrant administration of intrapartum antibiotics to at-risk women.

INTRODUCTION

Streptococcus agalactiae, widely known as group B streptococcus because of its possession of the Lancefield group B polysaccharide antigen, has been recognised as the leading cause of neonatal morbidity and mortality since the 1970s.1 Two distinct syndromes are described. Early-onset disease presents in the early neonatal period (0–6 days), often within a few hours of birth, and is caused by acquisition of the organism by the infant during childbirth from the genital tract of the mother. Late-onset disease occurs after the first week of life (7–90 days) and the organism is acquired after delivery either from the mother or nosocomially.

In most populations, the documented incidence of early-onset infection with group B streptococcus is reportedly 0.5–3 per 1000 live births.2 Several maternal and fetal risk factors for the development of the disease have been recognised. These include genital carriage of the organism, young maternal age, ethnicity, for example, black African or Caribbean, previous infant affected by this infection, multiple pregnancy, prolonged rupture of membranes, preterm delivery and intrapartum fever.3,4

In view of its mode of acquisition, various strategies to reduce the incidence of the disease have been documented. Indeed, in the USA, nationwide introduction of a policy of administration of intrapartum antibiotic prophylaxis to mothers with risk factors has coincided with a 70% reduction in the incidence of this disease.5,6

However, the use of intrapartum prophylaxis does have potential disadvantages, which include the possibility of anaphylaxis in the mother, the risk of changes to the microbial ecology of the mother and infant and the medicalisation of labour in addition to economic considerations. The economic cost–benefit of intervention strategies depends on several factors but mainly the prevalence of maternal carriage of the organism, the proportion of deliveries associated with recognised risk factors and the incidence of early-onset infection. American and Australian studies have demonstrated a cost–benefit to intervention in the respective study areas.7–9 In particular, Mohle-Boetani et al.7

a Health Protection Agency Collaborating Centre, Royal London Hospital, UK
b Health Protection Agency Specialist and Reference Microbiology Division, London, UK
Statistics Division, Health Protection Agency Communicable Disease Surveillance Centre, London, UK

Correspondence: Dr A. J. Mifsud, Health Protection Agency Collaborating Centre, Department of Microbiology, Royal London Hospital, 37 Ashfield Street, London, E1 1BB UK.

© RCOG 2004 BJOG: an International Journal of Obstetrics and Gynaecology
suggested that in their setting, a protocol based on universal screening is cost effective when the incidence of early-onset group B streptococcal infection exceeds 1.45 per 1000 live births, and a risk factor based approach is cost-beneficial when the disease incidence exceeds 0.65 per 1000 live births. Hence, the arguments in favour of the introduction of intrapartum antibiotic prophylaxis are dependent on the local incidence of the disease and the resulting mortality rate.

In the UK, the epidemiology of this condition is not well studied. To date, seven studies of the incidence of culture-proven invasive disease in the UK have been published since the 1970s, and the findings are summarised in Table 1.10–16 The observed incidence rates varied between 0.24 and 1.15 per 1000 live births. However, all studies except one undertaken 25 years ago (which yielded a result differing substantially from the remainder) were small, and all bar three studies were undertaken at single centres. A further weakness is that they have rarely included major urban and deprived areas. Indeed, US studies have shown that the incidence of this disease was highest in teenage mothers and among African-Americans (due to higher carriage rates).17 Early-onset group B streptococcal disease has significant mortality. US studies undertaken in the 1990s have shown a reduction in case-fatality rates to around 5% from 10% to 15% a decade earlier.17 Unsurprisingly, mortality is higher among preterm and small birthweight infants. UK studies have shown much higher case-fatality rates (Table 1). However, a population-based study from the North East of England showed rates broadly similar to those observed in the USA.18

In order to inform the development of guidance to reduce the incidence of this preventable disease, a multicentre retrospective study was set up in London under the auspices of the Health Protection Agency Group B Streptococcus Working Group, a multiprofessional group with representation from the Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Royal College of Paediatrics and Child Health, British Association of Perinatal Medicine, Association of Medical Microbiologists and Group B Strep Support (a UK charity). The aim was to determine the incidence of this infection in London, to estimate the burden of this disease in terms of morbidity, mortality and resource utilisation and to identify the prevalence of recognised risk factors in this urban, multiethnic population with a view to informing the preparation of guidance to reduce the incidence of the disease in the United Kingdom.

**METHODS**

A case of proven, invasive early-onset group B streptococcal disease was defined as the isolation of the organism from blood culture or other normally sterile site from an infant aged six days or younger.

Seven centres were recruited, five were tertiary referral centres with a neonatal intensive care unit (NICU) and a special care baby unit (SCBU), and the remaining two were located in district general hospitals with a SCBU. At each centre, the laboratory computer system was interrogated for all isolates of group B streptococcus from blood cultures, tissue or fluid specimens obtained from neonates aged six days or younger in the preceding 10 years, from January 1990 to December 1999, or for as long as computerised laboratory records were available. The hospital case notes for each infant and mother were obtained and examined for details of known maternal risk factors, namely, maternal age and ethnicity, previous infant with early-onset infection with GBS, multiple pregnancy, duration of rupture of membranes, gestational age of neonate at birth, intrapartum pyrexia and the clinical presentation of the infant at birth and outcome. Infants of women who had been referred to one of the centres for specialist care from another hospital were excluded, as were infants born outside the catchment areas for the seven hospitals. The birth cohorts for the respective centres were obtained from the Office of National Statistics (ONS). Data on multiple births and maternal age were obtained from Department of Health Hospital Episode Statistics (HES) and the ONS. Data on the

Table 1. Incidence and mortality from early-onset group B streptococcal infection in the United Kingdom.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Proven invasive early-onset disease</th>
<th>Birth cohort</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence (/1000 live births)</td>
<td>Mortality (/10,000 live births)</td>
<td>CFR (%)</td>
</tr>
<tr>
<td>Aberdeen</td>
<td>0.72</td>
<td>4.1</td>
<td>57</td>
</tr>
<tr>
<td>25 centres, E&amp;S</td>
<td>0.24</td>
<td>0.9</td>
<td>37</td>
</tr>
<tr>
<td>Northern Region</td>
<td>0.8</td>
<td>0.8</td>
<td>19</td>
</tr>
<tr>
<td>Oxford</td>
<td>0.56</td>
<td>1.1</td>
<td>19</td>
</tr>
<tr>
<td>Sunderland</td>
<td>0.95</td>
<td>1.1</td>
<td>19</td>
</tr>
<tr>
<td>Wessex</td>
<td>1.0</td>
<td>1.0</td>
<td>14</td>
</tr>
<tr>
<td>Bedfordshire</td>
<td>1.2</td>
<td>1.6</td>
<td>14</td>
</tr>
<tr>
<td>Northern Region</td>
<td>0.57</td>
<td>0.96</td>
<td>17</td>
</tr>
</tbody>
</table>

E&S = England and Scotland; CFR = case-fatality rate.

© RCOG 2004 *Br J Obstet Gynaecol* 111, pp. 1006–1011
proportion of the female population of child-bearing age (16–44 years), resident in the London Boroughs served by the seven hospitals, who were described as white, black (African, Caribbean, or ‘Other’) or from the Indian sub-continent (Indian, Pakistani or Bangladeshi), were obtained from the 1991 and the 2001 national censuses. Data on the proportion of deliveries that were preterm (before 37 weeks completed gestation) were obtained from HES or were complicated by duration of rupture of membranes greater than 24 hours, or pyrexia greater than 38°C were obtained from the literature.14

The precision of the estimated incidence rates within each risk factor categories were assessed by calculating the exact Poisson confidence intervals.19 Tests of association were performed using the likelihood ratio test within Poisson regression analysis, this analysis also providing estimates of incidence rate ratios. All analyses were performed using Stata version 7 (Release 7.0, Stata, College Station, Texas).

The study methodology was reviewed and approved by the Public Health Laboratory Service Ethics Committee (project number 1999/22).

RESULTS

Laboratory records were available for the whole 10-year period for five centres, for May 1990 to December 1999 for another centre and for five years (May 1995 onwards) for the seventh centre.

Notes were examined for 123 mother–baby pairs, 8 babies and 4 mothers. Neither set of notes could be located for the remaining five mothers and babies, but limited information was available from the hospital’s computer patient administration system for some of these patients.

Table 2. Incidence of and mortality from early-onset group B streptococcal disease at study participating centres.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Period *</th>
<th>Live births</th>
<th>Cases of EOGBS</th>
<th>Incidence rate ratio (95% CI)</th>
<th>Known survivors</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>Rate per 1000 live births (95% CI)</td>
<td>No.</td>
<td>CFR (%)</td>
</tr>
<tr>
<td>A</td>
<td>1990–1999</td>
<td>18,337</td>
<td>18</td>
<td>0.98 (0.58–1.55)</td>
<td>Reference</td>
<td>14</td>
</tr>
<tr>
<td>B</td>
<td>1990–1999</td>
<td>37,087</td>
<td>35</td>
<td>0.94 (0.66–1.31)</td>
<td>0.96 (0.54–1.7)</td>
<td>27</td>
</tr>
<tr>
<td>C</td>
<td>1995–1999</td>
<td>17,764</td>
<td>10</td>
<td>0.56 (0.27–1.04)</td>
<td>0.57 (0.26–1.2)</td>
<td>7</td>
</tr>
<tr>
<td>D</td>
<td>1990–1999</td>
<td>28,686</td>
<td>20</td>
<td>0.70 (0.43–1.08)</td>
<td>0.71 (0.38–1.3)</td>
<td>16</td>
</tr>
<tr>
<td>E</td>
<td>1990–1999</td>
<td>34,187</td>
<td>18</td>
<td>0.53 (0.31–0.83)</td>
<td>0.54 (0.28–1.0)</td>
<td>16</td>
</tr>
<tr>
<td>F</td>
<td>1990–1999</td>
<td>34,304</td>
<td>26</td>
<td>0.76 (0.50–1.11)</td>
<td>0.77 (0.42–1.4)</td>
<td>22</td>
</tr>
<tr>
<td>G</td>
<td>1990–1999</td>
<td>28,041</td>
<td>13</td>
<td>0.46 (0.25–0.79)</td>
<td>0.47 (0.23–0.96)</td>
<td>11</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>198,388</td>
<td>140</td>
<td>0.71 (0.59–0.83)</td>
<td>0.71 (0.59–0.83)</td>
<td>113</td>
</tr>
</tbody>
</table>

EOGBS = early-onset group B streptococcal disease; CI = confidence interval; CFR = case-fatality rate.

* January 1990–December 1999, unless otherwise stated.
Twenty-two babies are known to have died, giving a case-mortality rate of 15.7% or 1.12 per 10,000 live births (Table 2). These rates may be an under-estimate, as the outcome could not be ascertained with certainty in five cases where case notes were missing. There was no evidence of a temporal trend in case-fatality rate over the study period or between centres.

The prevalence of characteristics or recognised risk factors in the affected mothers and infants are given in Tables 3 and 4. The rate of disease in infants of mothers belonging to black ethnic groups was nearly three times greater than in mothers who described themselves as white ($P < 0.001$). The rate of disease among Indian subcontinent mothers was nearly twice as high as in infants of white mothers, but this difference was not statistically significant ($P = 0.054$).

Young maternal age was not associated with an increased risk of infection. Multiple pregnancy was associated with a nearly threefold increased risk of at least one infant being affected, but numbers were too small to correct for the possible confounding effect of prematurity or low birthweight. Delivery before 37 completed weeks of gestation, membrane rupture longer than 24 hours and intrapartum pyrexia greater than 38°C were all associated with between a 10- to 20-fold increased risk of development of infection with group B streptococcus.

Of 63 women who had had a urine sample collected during the antenatal period, usually at a booking clinic visit, group B streptococcus was isolated from four samples. Twenty-nine women had a genital swab collected antenatally at least one day pre-delivery, usually for clinical reasons; the organism was found in only eight. It should be noted that most swabs were high vaginal swabs, whereas optimal detection of carriage requires the collection of lower vaginal and rectal swabs, and culture of these samples in the laboratory should be performed using specialised enrichment culture media in order to avoid high false-negative results. During the study period, none of the laboratories employed a broth-enrichment step to process these samples.

One hundred and two (68%) of the mothers of 140 infants had at least one of the risk factors that are frequently indicated for intrapartum antibiotic prophylaxis, viz. previous infant affected by group B streptococcal infection (1), preterm delivery before 37 completed weeks of gestation (63), rupture of membranes greater than 24 hours (62) or intrapartum pyrexia at or above 38.5°C (11). The mothers of a further four infants (cumulatively 71%) might have been offered prophylaxis if the thresholds had been dropped to rupture of membranes prolonged beyond 18 hours and intrapartum pyrexia above 38°C. Only one of the infants that died did not have any of the risk factors that might have led to the offer of prophylaxis.

Thirty percent of women were given antibiotics intrapartum. However, in all cases, the choice of agent, dose and duration was quite different from the regimen currently recommended in the UK (http://www.hpa.org.uk/infections/topics_az/strepto/goodpracticeStrepto.pdf).20,21

Of 126 infants for whom detailed admission records were available was an inpatient for 19

### Table 3. Incidence of early-onset group B streptococcal infection in infants of mothers of various ethnic groups at study participating centres.

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Live births*</th>
<th>Cases of EOGBS</th>
<th>Rate per 1000 live births (95% CI)</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>129,297</td>
<td>53</td>
<td>0.41 (0.31–0.54)</td>
<td>Reference</td>
</tr>
<tr>
<td>Black</td>
<td>33,430</td>
<td>53</td>
<td>1.6 (1.2–2.07)</td>
<td>3.9 (2.6–5.7)</td>
</tr>
<tr>
<td>Indian subcontinent</td>
<td>22,272</td>
<td>14</td>
<td>0.63 (0.34–1.05)</td>
<td>1.5 (0.85–2.8)</td>
</tr>
</tbody>
</table>

EOGBS = early-onset group B streptococcal infection; CI = confidence interval.
* Estimated from population statistics.

### Table 4. Prevalence of recognised maternal risk factors for development of early-onset group B streptococcal disease in mothers and infants at study participating centres.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of affected mothers (%)</th>
<th>No. of unaffected mothers</th>
<th>Prevalence of characteristic or factor in general population (%)</th>
<th>Incidence rate ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age &lt;20 years</td>
<td>11 (9)</td>
<td>115</td>
<td>9.1*</td>
<td>0.96 (0.46–1.8)</td>
</tr>
<tr>
<td>Previously affected infant</td>
<td>1 (2)</td>
<td>54</td>
<td>0.214</td>
<td>9.33 (1.3–66.9)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>5 (4)</td>
<td>130</td>
<td>1.4*</td>
<td>2.73 (1.1–6.7)</td>
</tr>
<tr>
<td>Premature delivery &lt;37 completed weeks</td>
<td>63 (47)</td>
<td>72</td>
<td>7.0*</td>
<td>11.63 (8.3–16.3)</td>
</tr>
<tr>
<td>Membranes ruptured &gt;24 hours</td>
<td>62 (48)</td>
<td>67</td>
<td>7.914</td>
<td>10.8 (14.8–29.7)</td>
</tr>
<tr>
<td>Intrapartum pyrexia (&gt;38°C)</td>
<td>26 (19)</td>
<td>79</td>
<td>1.614</td>
<td>20.2 (13–31.5)</td>
</tr>
</tbody>
</table>

* Derived from national ONS data.
† Number of mothers without respective risk factor used as reference.
days, 16 days of which were spent in NICU or SCBU. Term infants spent an average of seven days on NICU or SCBU and a further five days on a general paediatric ward.

DISCUSSION

This study has confirmed that early-onset group B streptococcal disease causes substantial morbidity and mortality in London. Two of the centres with lower than average incidence rates had intrapartum prophylaxis policies in place. The rate of disease incidence is similar to that observed in other, usually smaller UK studies, but is considerably lower than the rate observed in the USA in the mid-1990s which prompted the introduction of guidelines intended to reduce the incidence of this disease. In contrast, the case-fatality rate of 15.6% is higher than that observed in the USA, but the overall mortality rate of 1.1 per 10,000 live births is similar to that observed in the USA prior to the widespread introduction of prophylaxis policies. The reason for this is unclear and there is no evidence to suggest that neonatal care in these predominantly tertiary referral centres is inferior to that in US hospitals. Embleton has made a similar observation in his recent study of the mortality of early-onset group B streptococcal disease in the Northern Region. In our study, while cases of in utero referrals to participating centres were excluded, it would be expected that difficult cases would not be referred elsewhere from five of the seven centres, as might be the case from many district general hospitals. We suggest the possibility that under-diagnosis of milder, usually non-fatal cases, due to a higher threshold in the UK, when compared with the USA, for collection of diagnostic samples from neonates might explain this phenomenon. Indeed, the likelihood of significant under-diagnosis of this infection has been suggested by other authors.

Both US and UK studies have highlighted that some 50% of cases of early-onset disease occurred in mothers without any risk factors, leading the authors of these papers to suggest that risk factor based prophylaxis policies would have a limited impact. Indeed, recently issued guidance in the US recommends universal screening with administration of intrapartum prophylaxis to all colonised women. This study suggests that in London, nearly three-quarters of all cases had at least one risk factor that might have led to prophylaxis being offered to the mother. Only one infant whose mother did not have any risk factor died, suggesting that such infants can be treated successfully more readily, in part, because of their greater resilience as birthweight of all of these infants was >2500 g.

Early-onset group B infection occurred nearly three times more frequently in infants born to women of black ethnicity compared with those born to white women. The denominator applied was the estimated population of women of child-bearing age, belonging to the various racial groups, in the respective London Boroughs derived from the 1991 and the 2001 censuses. Some have doubted the accuracy of these statistics and it is not known whether population changes occurred in a linear fashion during the 10-year period. Furthermore, correction for differences in the relative fertility of women of different ethnicity was not attempted.

Twins and higher multiple births have been recognised to be at increased risk of developing group B streptococcal infection. Low birthweight and prematurity undoubtedly play a role in this, but a prospective study demonstrated a significantly elevated risk of early-onset infection in twins, even when corrected for birthweight. Univariate analysis of data in our study is in keeping with this finding.

In spite of these caveats, this study concurs with previous observations that black ethnicity, as well as multiple birth, is associated with higher rates of early-onset group B streptococcal infection. We propose that consideration be given to adding these factors to the list of indications for intrapartum prophylaxis.

CONCLUSION

This study provides strong support for the introduction of interventions to reduce the incidence of early-onset group B streptococcal disease in the United Kingdom, particularly in those areas where the incidence of the disease is similar to that observed in London. Moreover, it reinforces previous studies showing that black ethnicity and multiple births are associated with this infection. We note that the Royal College of Obstetricians and Gynaecologists has recently issued guidance endorsing a risk factor based prophylaxis policy. Extrapolation from US cost effectiveness studies suggests that risk-based interventions are likely to be cost effective. While a screening approach would prevent a greater proportion of cases, a risk-based approach could be expected to prevent as many as two-thirds of cases, in particular, reducing the burden of this infection on premature and more susceptible infants. Further studies are needed to formally assess the long term sequelae of infection, in order to establish clearly whether more intensive interventions are warranted throughout the UK.

Acknowledgements

This study was undertaken under the auspices of the Health Protection Agency Group B Streptococcus Working Group and was funded by the Public Health Laboratory Service Small Scientific Initiatives Fund. The authors would like to thank obstetricians, midwives, paediatricians and microbiologists at all participating centres, particularly Drs A. Breathnach, L. Neville, B. Patel,
M. S. Shafi, N. Shetty and J. Wade. They would also like to thank Misses A. Freeth and J. Richards, study nurses, who undertook the bulk of the data collection.

Membership of Health Protection Agency Group B Streptococcal Working Group
Dr A. C. McCartney (chairman), Dr A. Efstratiou (scientific secretary), Ms C. Bates, Dr R. Feldman, Dr R. Fey, Dr P. Heath, Dr R. Hughes, Ms T. Lamagni, Dr A. J. Mifsud, Dr A. Nicoll, Dr S. Petrou, Dr E. Price, Dr J. Rennie and Dr A. Reynolds.

Conflict of interest
There was none.

References


Accepted 23 March 2004