What is the risk of beta-haemolytic streptococcal infection in obstetrics?: discussion paper[1]

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Fifty years ago Lancefield introduced her classification of the beta-haemolytic streptococci based on group-specific carbohydrate antigens. It was soon realized that streptococcal grouping had clinical as well as bacteriological significance, as the different groups were shown to possess differing pathogenic potential and to be associated with particular types of infection. The main groups associated with obstetric and neonatal disease are A, B and D, and to a lesser extent C and G. While the major part of this paper will concentrate on the group B streptococcus, I shall start by considering the current importance of groups A, C, G and D streptococci in obstetric practice.

Group A streptococci

These are the classical streptococcal pathogens. Although commonly associated with upper respiratory and skin infections, they have a long and infamous association with serious perinatal disease. In the years immediately before the antibiotic era, group A streptococci were a major cause of puerperal sepsis.

In the UK today, perinatal group A streptococcal sepsis is fortunately rare. Isolated cases and sporadic outbreaks still occur and may cause serious temporary local problems, but little more. The organism remains highly sensitive to benzylpenicillin which, despite the introduction of ever more expensive new beta-lactam antibiotics, still remains the drug of choice. There is, however, the danger of complacency. Even where the group A streptococcus is isolated in the absence of overt infection, particularly in the obstetric unit, it should be taken seriously. Mother or staff member should be kept away from other mothers and babies in the unit for a minimum of 24 hours. With appropriate antimicrobial therapy (benzylpenicillin or erythromycin), the risk to others in the unit should then be minimal. If more cases occur, staff and patients should be checked for upper respiratory carriage and it may be necessary to close the unit temporarily to new admissions.

The severity of group A streptococcal infection can easily be underestimated. Initially there may only be minimal abdominal tenderness, vaginal discharge, low-grade pyrexia and erythema around a wound site with a slight serous exudate. The group A streptococcus will spread rapidly along fascial planes and the infection may be more widespread than signs of inflammation indicate.

Although benzylpenicillin is highly active against the group A streptococcus, its efficacy will be impaired if there is a localized accumulation of pus. Early drainage is important and failure so to do is a common cause of apparent treatment failure. The temptation to change from parenteral to oral therapy as soon as the woman begins to respond should be resisted: too early a change can sometimes result in relapse, particularly if the original infection was severe.

Group C and G streptococci

The pathogenic potential of these organisms is much lower than that of the group A streptococcus. Grown on blood agar, they resemble the more virulent group A strains and it is important for the laboratory to distinguish them. In the absence of symptoms these

[1]Paper read to Section of Obstetrics & Gynaecology, 28 October 1983. Accepted 14 December 1983

0141–0768/84/040302–07/$01.00/0

streptococci do not normally need to be eradicated. They are commensals in the upper respiratory tract, and group G streptococci are also found in the gastrointestinal and genital tract. Recently there have been reports of neonatal sepsis caused by group G organisms (Khan *et al.* 1979, Baker 1974) and we have had such a case at St Mary's Hospital.

Group D streptococci

This group includes the enterococci (mainly *Streptococcus faecalis*). They are commensals of both the gastrointestinal and genital tracts and their isolation from a high vaginal swab is not usually of clinical significance. Although of low virulence, enterococci can cause ascending infection leading to chorioamnionitis, endometritis, and serious neonatal sepsis.

Their presence in the gastrointestinal tract is linked to their importance in urinary tract infections. Although not as common a cause of infection as *Escherichia coli,* they are important urinary tract pathogens. Urinary tract infections left untreated can affect the outcome of pregnancy and lead to pyelonephritis and renal scarring (Elder *et al.* 1971, Williams *et al.* 1978).

Unlike most other beta-haemolytic streptococci, the enterococci are relatively resistant to benzylpenicillin, with ampicillin or amoxycillin being the antibiotics of choice. The enterococci are also resistant to cephalosporins. Not only will the new, aggressively-marketed cephalosporins fail to cure enterococcal infections, but their widespread use in a unit may lead to the gradual emergence of these streptococci as significant nosocomial pathogens.

A rather different group D streptococcus, *Streptococcus bovis,* can also cause serious neonatal sepsis (Parker 1977).

Group B streptococci

Of these beta-haemolytic streptococci, the group A organisms are the most virulent and present the greatest risk of serious infection, while the enterococci are probably responsible for the greatest number of neonatal and maternal infections. However, another organism, the group B streptococcus (GBS), is easily the most important perinatal streptococcal pathogen.

Colebrook & Purdie (1937) were the first to describe systemic maternal GBS infection, while Brown (1939) produced the first report of neonatal septicaemia. However, between 1937 and 1957 only three cases of neonatal GBS infection appeared in the literature, compared with 21 cases of maternal sepsis (Parker 1977). In contrast, from 1958 to 1968 there were 82 reported cases of neonatal sepsis (Parker 1977). Since then, in both Western Europe and the USA, the numbers of reports of neonatal sepsis have increased. Today GBS are, with *E. coli,* the commonest neonatal bacterial pathogens. A recent survey in Britain gives an infection rate of 0.3 per thousand live births (Mayon White 1982). However, in some centres in the USA, GBS infection rates are ten times higher.

Is neonatal GBS infection a new disease or was it simply missed earlier? GBS are easy to grow on standard laboratory media. GBS beta-haemolysis is readily distinguished from that produced by group A, C and G streptococci. The grouping reagents have been available for many years. Against this must be set the clinical presentation of neonatal disease, particularly in the first 48 hours of life. The major symptoms are shock and respiratory distress and unless a diagnosis of infection is sought positively, it may be missed. Overall it seems unlikely that bacteriologists serving obstretric and neonatal units would have missed GBS. Given that a new pattern of disease may have emerged about 20 years ago, no adequate theory has been proposed to explain such a change.

With the natural concern with neonatal GBS sepsis, with its high mortality and poor response to chemotherapy, maternal GBS morbidity has been rather overlooked. It is difficult to obtain good figures for rates of perinatal maternal infection. In Britain there is no reporting system for GBS infections other than septicaemia and meningitis, and most evidence of GBS maternal morbidity is taken from local surveys and anecdote.

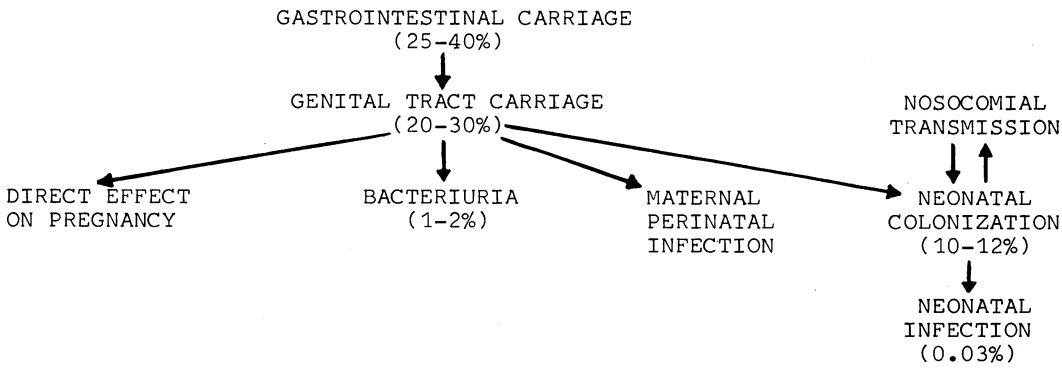

Figure 1. Epidemiological pattern of GBS colonization and infection in mother and baby

Epidemiology of group B streptococci

The epidemiological pattern of GBS colonization and infection in mother and baby is shown in Figure 1. A number of surveys have shown anorectal colonization rates to be higher than corresponding vaginal rates (Badri *et al.* 1977, Dillon *et al.* 1982), and the gastrointestinal tract and perineal skin is now thought to be the primary site of GBS colonization (Easmon *et al.* 1981*b*, Islam & Thomas 1980, Anthony *et al.* 1981). During pregnancy, anorectal and perineal carriage is the major factor in determining the pattern of vaginal colonization. Any attempt to screen for carriage must include anorectal or perineal swabs. The overall GBS carriage rate found in pregnancy will also depend on the following:

(1) The use of sensitive broth-enrichment techniques to detect low-level carriage (Baker & Barrett 1973).

(2) The number of sites sampled and the number of times sampled during pregnancy (Easmon *et al.* 1984).

(3) The background sexual activity of the population being studied. GBS carriage is broadly associated with the degree of sexual activity, although not linked to any specific sexually-transmitted disease (Christensen *et al.* 1974, Embil *et al.* 1978).

It is almost impossible to compare carriage rates obtained in different studies, as these important variables usually differ. However, in most populations about 20–30% of mothers will be colonized with GBS. In a survey that we have recently completed involving 1457 women (Easmon *et al.* 1984), the overall GBS carriage rate was 28%. In those women sampled once during pregnancy the rate was 23%; in those sampled four times this rose to nearly 34%.

The practical importance of this epidemiological information is three-fold: it defines the population in which maternal GBS morbidity will occur; it defines the minimum clinical and bacteriological effort needed for effective screening to predict intrapartum GBS carriage; intrapartum GBS carriage is the main source of organisms for early onset neonatal GBS sepsis.

Maternal morbidity from GBS infection

As shown in Figure 1, GBS can cause maternal morbidity in two ways: as a complication of bacteriuria and by tissue and blood stream infection during or after labour (or abortion).

Bacteriuria in pregnancy (3–8% of all pregnancies) is associated with premature labour and perinatal death (Williams *et al.* 1978). The main urinary tract pathogens are derived from the gastrointestinal and periurethral flora. In view of the high rate of GBS carriage among pregnant women, it is surprising that very little attention has been paid to the role of GBS in urinary tract infection. Wood & Dillon (1981) found that over 30% of significant bacteriurias in pregnancy were caused by GBS and that they were as common as those caused by *E. coli*. A small study we have carried out supports this figure (Easmon *et al.*

1984). Standard screening techniques used on antenatal urines are designed to detect enterobacteriaceae, enterococci and staphylococci, rather than GBS, and consequently they may be missed. No assessment has yet been made of the significance of GBS bacteriuria in pregnancy but, given the pathogenic potential of the organism, this needs to be done. GBS infections in general are more common in diabetics, as are urinary tract infections. The pregnant diabetic woman may, therefore, be particularly at risk from GBS, but this too needs assessment. There is no evidence that GBS colonization of the genital tract results in premature labour, premature rupture of membranes, intrauterine growth retardation or fetal death.

Ascending GBS infection can result in chorioamnionitis and endometritis. Callen *et al.* (1980) found that 67% of women harbouring GBS in the vagina had an intrapartum pyrexia of $\geqslant 38°C$ as compared with 10% of those who did not. We too have found a strong association between GBS carriage and intrapartum pyrexia (Easmon *et al.* 1984), while Beargie *et al.* (1975) and Gibbs *et al.* (1982) again found GBS to be a major cause of amnionitis and endometritis.

These studies dealt largely with vaginal deliveries. With caesarian section the GBS is also a major determinant of postoperative maternal morbidity (Minkoff *et al.* 1982).

GBS transmission from mother to baby

Between 20% and 30% of mothers carry GBS in the vagina during labour, and 10–12% of infants become colonized within the first two to three days of birth. However, only about 0.02% of babies become infected. Once GBS sepsis is established in the neonate, the mortality may be above 50% and antimicrobial therapy may have little effect on this. Prevention of infection is the ideal solution.

Transmission from mother to baby depends largely on the heaviness of maternal vaginal carriage (Ancona *et al.* 1980, Easmon *et al.* 1984). Neonatal infection is directly related to the heaviness of colonization and the number of sites colonized (Christensen *et al.* 1981). The cycle of mother/baby transmission can be broken by intrapartum systemic ampicillin or benzylpenicillin (Yow *et al.* 1979, Easmon *et al.* 1983*b*). Treatment earlier in pregnancy does not eradicate the organism, as might be expected with a gastrointestinal commensal (Gardner *et al.* 1979). Systemic antibiotics cannot reasonably be given to healthy mothers on the grounds that their babies have a one in three-to-four thousand chance of infection. Such an approach could only be used with effective bacteriological screening to define a high-risk group. Can bacteriological screening for GBS during pregnancy predict intrapartum carriage accurately and if so is such a practice cost effective?

For many years it was felt that vaginal colonization during pregnancy was so variable that sampling in pregnancy could not predict intrapartum carriage. However, studies such as those of Ferrieri *et al.* (1977) that came to this conclusion did not use sensitive enrichment cultural methods and used vaginal swabs only. I have already stressed the importance of the anorectal/perineal site as the prime determinant of colonization patterns during pregnancy.

Using enrichment cultures and anorectal and vaginal swabs, we have been able to predict 84% of intrapartum GBS carriage with swabs taken at 36 weeks, rising to 92% if swabs are taken at 28 weeks and 36 weeks (Easmon *et al.* 1984). It is, therefore, possible to predict intrapartum carriage with reasonable accuracy. The cost effectiveness of mass screening will depend on the neonatal infection rate. At 0.3 per thousand live births it would cost a bacteriology laboratory several thousand pounds in direct labour and consumable costs to predict one case of neonatal sepsis. The knowledge that such screening is effective may be of use in a more selective screening programme combined with other obstetric risk factors.

Nosocomial transmission of group B streptococci

Although maternal genital colonization is the most important source of GBS for neonates, in certain circumstances non-maternal hospital sources can provide an alternative route (Steere *et al.* 1975, Paredes *et al.* 1977). Good epidemiological surveys were limited by the poor discrimination of the GBS serotyping system. In 1980 Stringer reported a phage-typing

system that worked independently of serotyping and gave greatly improved levels of discrimination. This was used by Anthony *et al.* (1979) and Boyer *et al.* (1980) to demonstrate the spread of GBS from baby to baby in nurseries and a neonatal unit.

In collaboration with the Division of Hospital Infection at the Central Public Health Laboratory, my colleagues and I used phage typing to investigate nosocomial transmission of GBS in the Obstetric and Special Care Baby Units at St Mary's Hospital. At the time of the survey, building alterations had resulted in the concentration of all obstetric work in the District into the limited space provided by one rather than by two sites. We found that 36% of GBS-positive babies in the Obstetric Unit acquired the organism from non-maternal sources, compared with 9% in the Special Care Baby Unit. Colonized mother/baby pairs acted as the primary source of transmission, with staff playing a secondary role. In one case a doctor was the primary source of infant colonization; interestingly, this doctor was an upper respiratory tract GBS carrier. No infections resulted from nosocomial GBS spread, the babies were lightly colonized and all but one of those checked six weeks later were culture-negative (Easmon *et al.* 1981*a*, 1983*a*).

Neonatal group B streptococcal sepsis

Two forms of neonatal GBS sepsis are recognized. Early onset infection normally presents with respiratory distress and shock. If infection is not suspected, the diagnosis is all too easily missed. The very high mortality (often above 50%) is particularly associated with prematurity and with infection in the first 12 hours of life. Late-onset disease usually occurs after 5–7 days and is usually associated with meningitis. Although still a severe infection, late-onset sepsis has a lower morbidity than the early-onset form. In both forms neutropenia, which may signal depletion of marrow neutrophil reserves, is a poor prognostic sign.

Cultural diagnosis is too slow. The introduction of latex agglutination kits for the detection of GBS antigen in CSF blood, urine or gastric aspirate can give a diagnosis in a few minutes. Although sensitive to benzylpenicillin and ampicillin/amoxycillin, a few GBS strains show tolerance to these antibiotics, the concentration required for bacterial killing being more than 30 to 60 times greater than that needed for inhibition (standard sensitivity tests depend on inhibition of growth). For this reason aminoglycosides are often added to penicillins for therapy. New cephalosporins such as ceftriaxone have shown promise, particularly for meningitis.

Many babies are colonized with GBS, yet very few are infected. This suggests the presence of a few highly virulent strains and/or a few highly susceptible babies. The bacterial inoculum also seems to be important, as exposure to large numbers of streptococci for long periods of time – as seen with prolonged rupture of membranes and amnionitis – is a risk factor. Prematurity increases the severity of infection, but not the risk of acquisition. The host defence against GBS depends on opsonization, ingestion and killing of bacteria by phagocytic cells. Maternal IgC opsonic antibody that can cross the placenta is an important protective factor, and in most cases of serious neonatal sepsis neither mother nor baby has the relevant protective antibody (Baker & Kasper 1976).

In the absence of opsonic antibody, activation of the alternative complement pathway is the only way in which the neonate can recruit the vital phagocytic defences. However, the presence of surface sialic acid in the cell wall of many GBS prevents this method of complement activation and must be considered as an important virulence factor (Hastings & Easmon 1981).

It is probably no coincidence that *E. coli* type K1, the other major bacterial neonatal pathogen, also has surface sialic acid. No extracellular toxins have been shown to play any part in GBS disease.

Since antimicrobial therapy alone is of limited value, attention is now being paid to the use of granulocyte transfusions and the provision of antibody and complement as supplementary therapy. Maternal immunization with GBS vaccine is also being investigated in the USA.

Conclusions

Forty years ago the pattern of streptococcal disease in obstetric practice was completely different from that seen today. Group B organisms have replaced the group A streptococcus as the major pathogenic group. Looking to the future, the increased use of antibiotics may lead to the emergence of other streptococcal groups such as the enterococci. Group G streptococci seem to be capable of causing neonatal disease indistinguishable from that caused by GBS. Whether they too will increase in importance remains to be seen. No sooner do we learn how to combat one type of streptococcal sepsis than it is replaced by another. One thing seems certain: streptococcal infection of one sort or another will continue to be a problem for the obstetrician.

Acknowledgments: My work on group B streptococci has been supported by the Medical Research Council. I thank my colleagues in Bacteriology, Midwifery, Obstetrics and Paediatrics for their cooperation.

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