Antibiotic use and women in preterm labour

Preterm birth before 32 weeks' gestation is the leading cause of perinatal morbidity and mortality; the incidence appears to be rising and interventions to reduce the trend are urgently needed (Anonymous, 2006). Inflammation appears to be the final common pathway to preterm birth, causing uterine contractions, cervical ripening and rupture of the membranes; increased levels of pro-inflammatory cytokines are found in the myometrium, membranes and amniotic fluid of women in preterm labour and there is an associated influx of inflammatory cells into the uterus (Lindström and Bennett, 2005).

Infection has been proposed as a likely inflammatory stimulus; micro-organisms ascending the cervical canal or circulating in maternal blood can infect amniotic fluid, fetal membranes and the fetus and stimulate a localized inflammatory response via pattern-recognition receptors, e.g. Toll receptors (Goldenberg et al, 2008). Between 25 and 40% of preterm births might be caused by microbial infection although the true rate remains uncertain as the type of organisms implicated are difficult to culture by conventional means, but also because micro-organisms can be present in the fetal membranes without triggering an inflammatory response (Goldenberg et al, 2008).

Short-term outcomes following antibiotics for preterm labour

These data have lead to a number of studies investigating whether bacterial eradication using antibiotics can reduce the incidence of preterm birth and improve neonatal outcome. Two of the most influential of these studies, ORACLE I and II, were published in the *Lancet* 7 years ago (Kenyon et al, 2001a,b).

Women presenting with either preterm rupture of membranes or preterm labour were randomized to receive either erythromycin, co-amoxiclav, both antibiotics or placebo. ORACLE I showed that in women with preterm rupture of membranes, erythromycin treatment was associated with prolongation of pregnancy and reduction in neonatal morbidity, compared with women who did not receive erythromycin; while co-amoxiclav did prolong pregnancy it did not improve short-term neonatal outcomes and was associated with a higher incidence of neonatal necrotizing enterocolitis. On this basis erythromycin has become standard treatment for women presenting with preterm rupture of membranes. By contrast, antibiotic treatment of women presenting with preterm labour and intact membranes was not associated with prolongation of pregnancy or any improvement in either neonatal morbidity or mortality (ORACLE II; Kenyon et al, 2001b).

Long-term outcomes following antibiotics for preterm labour

A criticism of many trials to prevent preterm labour is that the primary outcome is prolongation of pregnancy, rather than beneficial effects on neonatal survival and morbidity. However, the ORACLE studies have recently demonstrated that even assessing short-term neonatal outcome, as was done in the original papers, is not enough. Wise funding decisions allowed the investigators to follow up surviving infants from the original study for 7 years and the results were recently published (Kenyon et al, 2008a,b). The data suggest that prescription of antibiotics for women with preterm rupture of membranes has little effect on the health of children at 7 years, i.e the initial benefits of treatment with erythromycin are not sustained.

More worryingly, erythromycin use in women in preterm labour with intact membranes was associated with an increase in functional impairment in their children (mainly mild), and cerebral palsy was more common when the mother had received either antibiotic, with the greatest risk observed in those who had received both antibiotics together. Overall the risk of cerebral palsy was low, e.g. 53 (3.3%) of 1611 receiving erythromycin *vs* 27 (1.7%) of 1562 that didn't (odds ratio 1.93, 95% confidence interval 1.2–3.1). The number needed to harm with erythromycin was 64 (95% confidence interval 37–209) and was with co-amoxiclav 79 (95% confidence interval 42–591).

Effects of antibiotic treatment

It would be wrong to conclude from these data, and other studies that have shown a negative impact of antibiotic use on preterm labour, that because antibiotics do not improve outcome bacteria do not play a role in the aetiology of preterm birth and neonatal morbidity. Although it is possible that antibiotics could cause cerebral palsy or preterm labour by a direct effect on the fetus or activation of inflammatory pathways in myometrium and membranes, this is less likely than that antibiotics affect the crucial link between bacteria and inflammation.

The presence of inflammatory cells in fetal membranes (chorioamnionitis) and elevated levels of pro-inflammatory cytokines in amniotic fluid or fetal blood have all been associated with damage to developing white matter and cerebral palsy (Royal College of Obstetricians and Gynaecologists, 2007). Although maternal antibiotic treatment might clear or suppress bacterial colonization it will not necessarily have an anti-inflammatory effect; in fact, it is possible that it could make matters worse, either by stimulating Toll receptors through release of immunogenic bacterial cell wall products and DNA, or by prolonging pregnancy and therefore fetal exposure to inflammatory molecules.

It is of interest that length of exposure to antibiotics in the ORACLE II study was fairly long, with 80–85% giving birth after 7 days; sub-group analysis suggested that it was those who completed their full 10-day course of antibiotics and then had a delay in delivery till nearer term that were at increased risk of cerebral palsy.

Implications for clinical practice

How do these data affect current obstetric practice? The exclusion criteria for both ORACLE studies included signs suggestive of overt clinical chorioamnionitis such as pyrexia, uterine tenderness, contractions or offensive discharge; in this scenario prompt treatment with broad-spectrum antibiotics is indicated. The rationale of therapy is not to prolong pregnancy, indeed delivery might be expedited; it is mainly to protect the mother against the risks of septicaemia, still a cause of maternal mortality in the UK, and to a lesser extent to provide antibiotic cover for the fetus. Similarly, antibiotic treatment should not be withheld for other maternal infections, such as pyelonephritis, during the second or third trimesters of pregnancy. However, the ORACLE follow-up studies suggest that clinicians should be cautious before using antibiotics to prolong pregnancy when there are no signs of infection.

Although ORACLE I did not show a harmful effect of antibiotics in women with preterm rupture of membranes, and obstetricians may be encouraged by the short-term benefits reported in the original trial, it is hard to see a continued routine role for erythromycin in women with preterm rupture of membranes when there are potential risks to widespread antibiotic usage, and no long-term benefits were demonstrated. Although the direct clinical impact of the findings from ORACLE II are limited by the fact that antibiotics are not routinely prescribed for women in preterm labour with intact membranes, the data have wider implications concerning the use of antibiotics for the prevention of preterm birth, particularly when the effect on maternal and/or fetal inflammatory pathways is unknown.

Future studies

An inviting concept is that antibiotic use should be targeted at known infections, identified by amniocentesis or swabs, and should be combined with immune modulation, to decrease the inflammatory sequelae in fetus and neonate. However, the ORACLE data suggest that such a combined approach should only be trialled clinically after extensive basic research to better understand the links between bacterial colonization, inflammation and neonatal injury; and also that long-term follow up should be a condition of any such trial. BJHM

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KEY POINTS

- Localized intrauterine inflammation is the main cause of preterm delivery.
- Intrauterine microbial infection is one cause of inflammation.
- Erythromycin prolongs pregnancy and improves short-term neonatal outcome following preterm rupture of the membranes but these benefits do not translate into long-term improvement in outcome.
- Antibiotics for treatment of preterm labour with intact membranes have no short-term benefit but are associated with a higher incidence of cerebral palsy in surviving neonates.
- Broad-spectrum antibiotics are indicated for treatment of clinical chorioamnionitis.