

ERYTHROMYCIN (Comment)

Seven year outcomes from the ORACLE trial

The ORACLE trial was one of the largest and most ambitious perinatal trials ever funded when it was first launched by the Medical Research Council in the UK in 1994. It was designed to look at the potential benefit of giving prophylactic broad-spectrum antibiotic treatment to over 11,100 women who were threatening to go into preterm labour. The trial randomised these women into four groups: a quarter got 250 mg of erythromycin, a quarter got 375 mg of amoxicillin-clavulanate (co-amoxiclav), a quarter got both, and a quarter merely got an oral placebo four times a day for ten days, or until delivery (whichever was the sooner).

There were 4,826 women whose membranes had already ruptured at trial entry, and another 6,295 who seemed to be in otherwise unexplained preterm labour. In a far-sighted move the MRC also committed itself to funding the seven year follow up of all the 8,800 babies recruited into the trial in the UK.

The **early** outcome of this trial, published in 2001, showed that antibiotic treatment was of some benefit to both the mother and the baby when there was preterm pre-labour rupture of membranes (PPROM), but none when there was not. In singleton pregnancies with PPROM the prophylactic use of erythromycin was associated with a significant reduction in the risk of the trial's predefined primary outcome (babies who died, developed a serious cerebral abnormality on ultrasound, or severe persistent oxygen dependency). It was also associated with some prolongation of pregnancy, and some reduction in neonatal morbidity. Treatment with co-amoxiclav in PPROM, on the other hand, was not associated with any significant difference in the trial's primary endpoint. It did seem to prolong pregnancy, but it was also associated with an inexplicable excess of neonatal necrotising enterocolitis (NEC). UK Obstetric guidelines have, as a result, advocated the use of erythromycin for several years now where there is preterm pre-labour rupture of the membranes even though, for reasons that have never been explained, the difference in the trial's primary endpoint only became statistically significant when the analysis was limited to what happened in singleton pregnancy.

Very impressively, those responsible for this study managed to retain contact with almost three quarters of the UK children until they were at least seven years old, and a report on the **long term** outcome was finally published in the *Lancet* in October 2008. The trial has come up with some clear findings, and the clinical implications are also clear even though people are finding it hard to explain *why* the trial came up with the finding that it did. In those preterm pregnancies where there was pre-labour rupture of membranes treatment with erythromycin did some short term good and there were no adverse late consequences. However when the membranes were intact at recruitment, treatment did no good even in the short term, and treatment was associated with a small but significant excess of disability, including cerebral palsy, in the survivors.

There are a number of other outcomes that seem equally clear cut, but equally hard to explain and quite unexpected. We don't know why antibiotic treatment seemed to prolong labour in singleton pregnancy, but not in multiple pregnancy. We do not have any idea why pre-delivery treatment with co-amoxiclav seemed to make NEC more likely, and it is hard to understand why giving erythromycin before delivery should be associated with an excess of cerebral palsy when the membranes have not ruptured, but with no such excess when they have. The fact that a rather similar excess was seen when co-amoxiclav was used in preterm labour with intact membranes, and that the risk seemed particularly high in those who received both antibiotics, seems to suggest that the risk is not just linked to the use of one particular group of antibiotics, and that it may be better to avoid *any* antibiotic treatment before delivery when it is not necessary.

However, even though it is difficult to explain why this trial should have come up with the findings it did, it is very clear what should be done now that the outcome is known. The conclusion has to be that antibiotics should never be used in an attempt to prolong labour when the membranes are intact – there are other more effective strategies. The only probable exception to that generalisation would currently seem to be the use of clindamycin (q.v.) where there is proven bacterial vaginosis. It is equally doubtful whether low dose oral treatment with a broad spectrum antibiotic is really justified when the membranes have ruptured either – the main focus here should, for the moment, be on the vigorous treatment of the minority of women where there is overt evidence of infection, and on the short term use of penicillin just during delivery itself to cover the risk associated with intrapartum group B streptococcal infection, or with both penicillin and gentamicin when labour starts before 35 weeks gestation and the membranes are known to have ruptured at least 6 hours before the onset of labour, as is advocated in the paragraph on antibiotic use during labour in this Formulary's current monograph on ampicillin.

Royal College of Obstetricians and Gynaecologists. *Preterm prelabour rupture of the membranes*. Green Top Guideline No 44. London : Royal College of Obstetricians and Gynaecologists, 2006.

Kenyon S, Pike K, Jones DR, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. *Lancet* 2008;**372**:1310–8. [RCT]

Kenyon S, Pike K, Jones DR, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008;**372**:1319–27. [RCT]

Bedford Russell AR, Steer PJ. Antibiotics in preterm labour – the ORACLE speaks. [Editorial] *Lancet* 2008;**372**:1276–8.

Donaldson L. Oracle children's study. Letter from the Chief Medical Officer. London: Department of Health, 16 September 2008.