

ERYTHROMYCIN (Commentary)

Use in preterm prelabour rupture of membranes

Preterm prelabour rupture of the fetal membranes (pPROM) is the main antecedent factor in a third of all preterm birth. Progressive weakening of the fetal membranes often precedes rupture while, in a third of cases, there is evidence of subclinical chorioamnionitis. Unfortunately trials to date suggest that early prophylactic treatment using metronidazole (q.v.) does not reduce the risk of preterm birth in women with asymptomatic vaginosis but intact membranes. Indeed it may actually increase it where there is trichomonas infection. Clindamycin may be more effective in this situation according to one recently published trial.

Where premature membrane rupture *has* already occurred, antibiotic treatment can delay delivery for a few days in at least some women. The Oracle trial recruited 11,121 women between 1994 and 2000 into a study designed to confirm that antibiotic treatment could delay delivery but also, more importantly, to determine whether it had any measurable impact on maternal and neonatal outcomes. It should be noted that the study only recruited women in whom there was no overt indication for antibiotic treatment. Many obstetricians would hold group B streptococcal carriage to be an indication for treatment, but such screening was not common in the UK at the time this study was done.

Erythromycin and co-amoxiclav (a combination of amoxicillin and clavulanic acid) were studied in this large placebo controlled trial. Both strategies delayed delivery in a minority of women by at least two days and, in a few, for over a week. The main index of neonatal outcome was a composite measure of chronic lung disease (prolonged oxygen dependency), major cerebral ultrasound abnormality or death. Treatment with erythromycin on its own was, using this measure, the only beneficial strategy and, even here, the difference in outcome only reached statistical significance when the analysis was limited to singleton birth (which had not been a pre-defined study outcome). Treatment with erythromycin also reduced the incidence of neonatal sepsis. There was also a marginal reduction in the use of exogenous surfactant. Treatment with co-amoxiclav was associated with no such advantage, and was associated with a significant increase in the incidence of necrotising enterocolitis (as outlined briefly in the monograph on amoxicillin). Ultrasound findings are not, in themselves, a reliable surrogate measure of long term developmental outcome, so it will only become clear whether treatment was really of measurable long term benefit when follow up is complete.

It can be concluded that no form of antibiotic treatment makes very much difference to the long term outcome of pregnancy in women with pPROM but no sign of overt infection. Erythromycin is the best studied antibiotic to use when treatment does seem indicated, but should not replace attempts to identify the presence of a specific bacterial pathogen. However, once it is clear that the woman is in active labour, there are strong grounds for giving antibiotics if pregnancy has not yet lasted 34 weeks to minimise the risk of the baby becoming septicaemic during delivery (as outlined in the monograph on penicillin). See:

Carey JC, Klebanoff MA, Hauth JC, *et al.* Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med* 2000;**342**:534–40. [RCT]

Kenyon AL, Taylor DJ, Tarnow-Mordi W for the ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001;**357**:979–88. [RCT] (See also **358**:502–4 and 1184–5.)

Klebanoff MA, Carey JC, Hauth JC, *et al.* Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic trichomonas vaginalis infection. *N Engl J Med* 2001;**345**:487–93. [RCT]

Ugwamadu A, Manyonda I, Reid F, *et al.* Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. *Lancet* 2003;**361**:983–8. [RCT]

Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm premature rupture of the membranes: a systematic review. *Obstet Gynecol* 2004;**104**:1051–7. [SR]

Neonatal pharmacokinetics

The neonatal half life is not affected by the route of administration, or by gestational or postnatal age, although the estolate salt (which is no longer available in the UK) seems to be better absorbed than the ethylsuccinate salt. See:

Burns L, Hodgman J. Studies of prematures given erythromycin estolate. *Am J Dis Child* 1963;**106**:280–8.

Patamasuon P, Kaojarem S, Kusmiesz H, *et al.* Pharmacokinetics of erythromycin ethylsuccinate and estolate in infants under 4 months of age. *Antimicrob Agents Chemother* 1981;**19**:736–9.

Ginsburg CM. Pharmacology of erythromycin in infants and children. *Pediatr Infect Dis J* 1986;**5**:124–9.

Waites KB, Sims PJ, Crouse DT, *et al.* Serum concentrations of erythromycin after intravenous infusion in preterm neonates treated for *Ureaplasma urealyticum* infection. *Pediatr Infect Dis J* 1994;**13**:287–93.

Cont over

Complications of neonatal use

There are reports of acute bradycardia developing in four very preterm babies given erythromycin as a 30 minute IV infusion. One baby died, and in at least one baby there was evidence of QT prolongation. Sustained high dose oral use (an average of 50 mg/kg a day for more than ten days) was also associated with a ten fold increase the risk of hypertrophic pyloric stenosis in two recent case control studies. See:

Farrar HC, Walsh-Sukys MC, Kyllonon K, Blumer JL. Cardiac toxicity associated with intravenous erythromycin lactobionate: two case reports and a review of the literature. *Pediatr Inf Dis J* 1993;**12**:688–91.

Gouyon JB, Benoit A, Btremieux P, *et al.* Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994;**13**:840–1.

Honiein MA, Paulozzi LJ, Himelright IM, *et al.* Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet* 1999;**344**:2101–5.

Mahon BE, Ropsenman MB, Kleiman MB. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. *J Pediatr* 2001;**139**:380–4.

Cooper WO, Griffin MR, Arbogast P, *et al.* Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 2002;**156**:647–50.

Sorensen HT, Skriver MV, Pedersen L, *et al.* Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. *Scand J infect Dis* 2003;**35**:104–6.

Use to improve neonatal gut motility

A number of studies have found that erythromycin is of help in selected babies with gut motility problems. While **routine** use did not reduce the time it took for babies of less than 30 weeks gestation to become fully enterally (tube) fed in two recent controlled trials, a small dose (2.5 mg/kg by mouth once every 6 hours) did have a small but measurable effect in the trial of routine use reported by Oei and Lui in 2001. Full enteral nutrition was achieved after 6.0 rather than 7.9 days. In **selected** babies with food intolerance the effect can be more marked. Treatment with 50 mg/kg a day halved the time it took for full enteral nutrition to be achieved in babies still taking less than 75 ml/kg of milk a day by mouth in the trial reported by Ng in 2001. It was also halved in a trial that used half this dose (Nuntnarumit *et al*, 2006), and in a trial (Cairns *et al*, 2002) that used an even smaller dose (12 mg/kg a day). Similarly, in a non-blinded study, Nogami *et al* (2001) found that an IV dose of as little as 1-2 mg/kg 3 times a day reduced the time it took for babies still intolerant of feeds 5 days after birth to tolerate milk feeds. An intake of 100 ml/kg a day was achieved after 15 days in the babies given erythromycin, and after 23 days in the control group. The Cochrane review has not been updated since 2001, but a rather more up to date systematic review was published by Patole *et al.* in 2005. A controlled trial using a dose of 3 mg/kg by mouth once every 6 hours in babies of more than 31 weeks gestation with gastroschisis **is** currently recruiting in the UK. Treatment is started 5 days after primary wall closure. For details contact the paediatric surgeons in Leeds or Birmingham. See:

Itoh Z, Naklaya M, Susuki T, *et al.* Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. *Am J Physiol* 1984;**247**:G688–94.

Otterson MF, Sarna SK. Gastrointestinal motor effects of erythromycin. *Am J Physiol* 1990;**259**:G355–63.

Tomomasa T, Miyazak M, Koizumi, *et al.* Erythromycin increases gastric antral motility in human premature infants. *Biol Neonat* 1993;**63**:349–52.

Kubota M, Nakamura T, Motokura T, *et al.* Erythromycin improves gastrointestinal motility in extremely low birthweight infants. *Acta Paediatr Jpn* 1994;**36**:198–201.

Simkiss DE, Adams IP, Myrdal U, *et al.* Erythromycin in neonatal postoperative intestinal dysmotility. *Arch Dis Child* 1994;**71**:F128–9.

Jadcherla SR, Klee G, Berseth CL. Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res* 1997;**42**:365–9.

Stenson BJ, Middlemist L, Lyon AJ. Influence of erythromycin on establishment of feeding in preterm infants: observations from a randomised controlled trial. *Arch Dis Child* 1998;**79**:F212–4. [RCT]

Patole SK, Almonte R, Kadalraja R, *et al.* Can prophylactic oral erythromycin reduce time to full enteral feeds in preterm neonates. *Int J Clin Pract* 2000;**54**:504–8. [RCT]

Nogami K, Nishikubo T, Minowa H, *et al.* Intravenous low-dose erythromycin administration for infants with feeding intolerance. *Pediatr Internat* 2001;**43**:605–10.

Oei J, Lui K. A placebo-controlled trial of low-dose erythromycin to promote feed tolerance in preterm infants. *Acta Paediatr* 2001;**90**:904–8. [RCT]

Ng PC, So KW, Fung KSC, *et al.* Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child* 2001;**84**:F177–82. [RCT]

Cairns P, Craig S, Tubman R, *et al.* Randomised controlled trial of low dose erythromycin in preterm infants with feed intolerance. [Abstract] *Pediatr Res* 2002:A2209. [RCT]

El Hennawy AA, Sparks JW, Armentrout D, *et al.* Erythromycin fails to improve feeding outcome in feeding-intolerant preterm infants. *J Pediatr Gastroenterol Nutr* 2003;**37**:281–6. [RCT]

Ng SC, Gomez JM, Rajadurai VS, *et al.* Establishing enteral feeding in preterm infants with feeding intolerance: a randomized controlled study of low-dose erythromycin. *J Pediatr Gastroenterol Nutr* 2003;**37**:554–8. [RCT]

Patole S, Rao S, Doherty D. Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child* 2005;**90**:F301–6. [SR]

Nuntnarumit P, Kiatchoosakun P, Tantipparpa W, *et al.* Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006;**148**:600–5. [RCT]

Management of maternal chlamydial infection

The health implications of asymptomatic chlamydial infection in adult life are more serious than are generally appreciated, and screening programmes are probably worthy of support in sexually active young adults. See:

Rettig PJ. Perinatal infections with *Chlamydia trachomatis*. *Clin Perinatol* 1988;**15**:321–50.

Scholes D, Stergachis A, Heidrich MD, *et al*. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *N Engl J Med* 1996;**334**:1362–6.

Davies HD, Wang EE. Periodic health examinations, 1996 update: 2. Screening for chlamydial infections. Canadian Task Force on the Periodic Health Examination. *Can Med Assoc J* 1996;**154**:1631–44. [SR]

Department of Health. Report of the CMO's Expert Advisory Group on *Chlamydia trachomatis*. London: Department of Health, 1998.

Anon. Screening to prevent pelvic inflammatory disease from *Chlamydia trachomatis* genital infection. *J Med Screen* 2000;**7**:55.

Use to prevent whooping cough cross infection

Treatment with erythromycin rapidly renders infected patients culture negative. A recent uncontrolled study has shown that this is also true of a short course of azithromycin. On the other hand, a well conducted placebo-controlled trial showed that oral use for 7 or 14 days in children exposed to whooping cough infection did *not* reduce the number of babies going on to develop features typical of whooping cough infection (although it did reduce the number from whom the organism was cultured). This may be because cross infection often occurs early in the illness before its nature is recognised and a diagnosis made. Oral treatment caused some diarrhoea and abdominal cramp. Sustained high dose use in the first few weeks of life may also increase the risk of the baby developing hypertrophic pyloric stenosis (see above). On the other hand, treatment from birth in mothers with proven infection at delivery seems, in uncontrolled studies, to prevent the baby becoming infected. See:

Granström G, Sterner G, Nord CE, *et al*. Use of erythromycin to prevent pertussis in newborns of mothers with pertussis. *J Infect Dis* 1987;**155**:1210–4.

Halperin SA, Bortolussi R, Langley, JM *et al*. A randomised placebo-controlled trial of erythromycin estolate chemoprophylaxis for household contacts of children with culture-positive *Bordetella pertussis* infection. *Pediatrics* 1999;**104**:e42.

Pichichero ME, Hoeger WJ, Casey JR. Azithromycin for the treatment of pertussis. *Pediatr Infect Dis J* 2003;**22**:847–9.

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