Selected Summary

Lessons from the ORACLE Children Studies (OCS): Antibiotics for premature rupture of membranes and preterm labour— To use or not to use?

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Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, Taylor DJ. (Reproductive Sciences Section, Cancer Studies and Molecular Medicine and Health Sciences Department, University of Leicester, Leicester, UK; National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK; Academic Division of Child Health, University of Nottingham, Nottingham, UK; Great Ormond Street Hospital for Children and Institute of Child Health, University College London, London, UK.) 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.

SUMMARY

These two studies, called the ORACLE Children Studies (OCS)–I and II, are the culmination of 7 years' follow up of the original trials that evaluated the use of erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) in 2 groups of pregnant women using a factorial randomized design. The first group (ORACLE I trial) consisted of pregnant women with preterm premature rupture of membranes (PPROM) and the second group (ORACLE II trial) consisted of those presenting with spontaneous preterm labour (SPL). These trials found that:

1. In women with PPROM, the use of erythromycin led to prolongation of pregnancy as well as decreased the risk of death or major cerebral abnormality or chronic lung disease in the neonatal period, whereas the use of co-amoxiclav increased the incidence of neonatal necrotizing enterocolitis in these infants;[1] and
2. In women with SPL the use of neither antibiotic was associated with any improvement in neonatal mortality or morbidity.[2]

The aim of these studies was to assess the long term effects on children exposed to these interventions. These studies began in 2002 and sought follow up information of children at 7 years of age who were born to women who participated in the ORACLE I and II studies. Children were traced with the help of the UK Office of National Statistics and by contact with their family doctors. Contact details of surviving children were obtained from the National Health Service (NHS) National Strategic Tracing Service. For those children who were not 7 years of age at the initial invitation, contact was maintained from 2001 onwards with birthday cards, newsletters, change of address cards and through a website. The West Midlands Multi-centre Research and Ethics Committee approved the study and the University of Leicester, UK, sponsored the OCS. Oversight was provided by an independent trial steering committee and data monitoring committee. Those involved in tracing and data entry remained blind to the allocated treatment.

Data were collected with a parent-completion postal questionnaire. This comprised the Health utilities index[3] from which the Multi-attribute health status (MAHS) is derived, the Strengths and difficulties questionnaire, hospital admissions and specific medical conditions. The primary outcome was defined as the presence of any level of functional impairment (severe, moderate or mild) derived from the mark III MAHS classification system within any of the individual attributes of vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. The overall level of functional impairment was determined by their worst score in any attribute. Secondary outcomes were the presence of 3 or more abnormal attributes and the degree of functional impairment within the individual domains, the number of deaths, the frequency of specific medical conditions and hospital admissions. The size of the study was predefined by the number of women recruited to the ORACLE trials.

Results

OCS I. The outcome was determined for 3298 eligible children (75%). There was no difference in the proportion of children with functional impairment after prescription of erythromycin (with or without co-amoxiclav) compared with those born to mothers who received no erythromycin for PPROM (38.3% *v*. 40.4%, OR 0.91, 95% CI: 0.79–1.05). Similarly, prescription of co-amoxiclav (with or without erythromycin) also did not affect the incidence of functional impairment at 7 years of age (40.6% *v*. 38.1%, OR 1.11, 95% CI: 0.96–1.28). Neither antibiotic had a significant effect on the overall level of behavioural difficulties experienced or on specific medical conditions.

OCS II. Outcome was determined for 3196 eligible children (71%). Overall, a greater proportion of children whose mothers had been prescribed erythromycin (with or without co-amoxiclav) had functional impairment than did those whose mothers had received no erythromycin for SPL (42.3% *v*. 38.3%, OR 1.18, 95% CI: 1.02–1.37). In contrast, the use of co-amoxiclav (with or without erythromycin) had no effect on the proportion of children with functional impairment (40.7% *v*. 40%, OR 1.03, 95% CI: 0.89–1.19). No effects were seen with either antibiotic on the number of deaths, other medical conditions, behavioural patterns or educational attainment. However, more children whose mothers had received erythromycin or co-amoxiclav developed cerebral palsy than did those born to mothers who received no erythromycin or no co-amoxiclav, respectively (erythromycin 3.3% *v*. 1.7%, OR 1.93, 95% CI: 1.21–3.09, number needed to harm (NNH) 64; co-amoxiclav 3.2% *v*. 1.9%; OR 1.69, 95% CI: 1.07–2.67, NNH 79). There is also evidence to suggest an additive effect on cerebral palsy when both the antibiotics were given together.

COMMENT

Prematurity, defined as birth of an infant before 37 completed weeks of gestation, remains an important cause of neonatal

mortality and morbidity. Estimates for the year 2000 of the distribution of direct causes of death indicate that preterm birth accounts for 28% of neonatal deaths.[4] Given that infections, the other leading cause of neonatal deaths, are distinctly more common in preterm neonates one can safely assume that prematurity is the major determinant of neonatal mortality. Moreover, infants who are born premature are at high risk of neonatal morbidities such as chronic lung disease, retinopathy of prematurity, intraventricular haemorrhage, periventricular leucomalacia as well as long term adverse neurodevelopmental outcomes such as cerebral palsy (CP), mental retardation, and behavioural and cognitive impairment.

The high risk of mortality and morbidity in preterm infants stimulated perinatologists to explore different strategies for prevention of prematurity. One such strategy was to administer antibiotics in women at risk for preterm delivery, either following spontaneous preterm labour (SPL) or preterm premature rupture of membranes (PPROM). Studies that showed a strong relationship between occult upper genital tract infection and PPROM/SPL (about 30% and 20% of cases, respectively) prompted investigators to evaluate this strategy in randomized clinical trials. The results of the largest and most important studies in this regard—the ORACLE I and II[1,2]—paved way for the current recommendation of using erythromycin (250 mg 6 hourly per oral for 10 days) in women with PPROM and no antibiotics for women with SPL and intact membranes. The investigators had planned a follow up study of childhood development and disability in infants born to these women, the results of which have been reported in these papers.

The ORACLE Children Studies (OCS) I and II are the culmination of an extensive and coordinated effort by researchers of the original trials. The 7-year follow up has been well planned and executed with the help of various national organizations of the UK. Though the studies have some methodological issues, in particular low follow up rates (70%–75%) and use of a parental questionnaire for determining the outcomes, the huge painstaking effort remains commendable. The results of these studies provide some important insights about the use of antibiotics in women at risk for preterm labour: first, use of erythromycin in women with PPROM seems to have little effect on the outcomes of children at 7 years of age. Second, the risk of cerebral palsy in children born to women with SPL is increased after use of either antibiotic while the risk of functional impairment is increased after the use of erythromycin. Third, there is a slightly higher incidence of bowel disorders with both co-amoxiclav (OCS I: OR 1.71, 95% CI: 1.05–2.79) and erythromycin (OCS II: OR 1.66, 95% CI: 1.10–2.49).

It is difficult to explain why the use of erythromycin in women with PPROM did not lead to any beneficial outcomes despite resulting in short term improvement in the neonatal period.[1] Similarly, the mechanism behind the adverse effects of both the drugs in children born to women with spontaneous preterm labour also needs to be elucidated. The possible mechanisms include:

1. *Failure to eradicate occult infection*. Unlike women with clinical chorioamnionitis who are treated with high dose intravenous antibiotics (usually a combination of cephalosporin and aminoglycosides), these women with suspected infection received only low doses of oral antibiotics. Moreover, many of these women (especially those with PPROM) received antibiotics for less than a week. This could have led to suppression of infection and not its eradication. On the other hand, in women whose pregnancy was prolonged with use of these antibiotics, continued exposure to low grade infection could have resulted in adverse outcomes such as cerebral palsy. This is especially true for women with SPL because about two-thirds of them delivered at term.
2. *Inflammation due to other causes*. Elevated cord levels of interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-alpha have been strongly associated with long term adverse outcomes such as cerebral palsy in preterm infants.[5] However, the levels of these inflammatory markers could increase due to reasons other than infection also. In such cases, antibiotics would be of no help.
3. *Direct toxic effects of drugs*. The rapidly developing foetal brain is vulnerable to the toxic effects of various drugs. Though the antibiotics used in the trials are considered to be safe, a potentially harmful effect cannot be ruled out. Similarly, antibiotics are known to affect the foetal gut flora and alter immune tolerance which could predispose them to allergic and autoimmune diseases in later life.[6] This could possibly explain the high incidence of bowel problems seen in these children.

Do these results warrant a change in the existing antibiotic policy?

After publication of these studies, the Royal College of Obstetricians and Gynaecologists (RCOG) has come out with a statement endorsing the current antibiotic policy of using erythromycin for women with PPROM and no antibiotics for women with SPL.[7] This seems reasonable because the use of erythromycin improves the short term neonatal outcomes as well as reduces the need for antibiotic therapy in mothers with clinical chorioamnionitis.[1] However, the lack of long term beneficial outcomes and the potential to cause direct toxic effects have prompted a few experts in the field to caution against the use of antibiotics in all women with PPROM.[8] Since the majority of women (about two-thirds) with PPROM would not have any infection but would still be treated with antibiotics, they advocate a more cautious approach that involves identifying and treating only those with proven upper genital tract infection (by either amniotic fluid cultures or polymerase chain reaction [PCR] techniques). These women could be treated with intravenous antibiotics so as to eradicate the infection. As the above-mentioned tests might not be available in most centres, it is essential to develop sensitive screening tests that can be employed at the bedside for the diagnosis of infections. Future trials should evaluate the usefulness of this approach as well as the efficacy of other antibiotic regimens especially in India where the organisms may be different. Until then, the existing policy of prescribing erythromycin to all women with PPROM can be continued.

REFERENCES

1 Kenyon SL, Taylor DJ, Tarnow-Mordi W; ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: The ORACLE I randomised trial. *Lancet* 2001;**357:**979–88. Erratum in: *Lancet* 2001;**358:**156.

2 Kenyon SL, Taylor DJ, Tarnow-Mordi W; ORACLE Collaborative Group. Broad-spectrum antibiotics for spontaneous preterm labour: The ORACLE II randomised trial. *Lancet* 2001;**357:**989–94.

3 Saigal S, Rosenbaum P, Stoskopf B, Hoult L, Furlong W, Feeny D, *et al.* Comprehensive assessment of the health status of extremely low birth weight children at eight years of age: Comparison with a reference group. *J Pediatr* 1994;**125:**411–17.

4 Zupan J, Aahman E. *Perinatal mortality for the year 2000: Estimates developed by WHO*. Geneva:World Health Organization; 2005.

5 Yoon BH, Romero R, Yang SH, Jun JK, Kim IO, Choi JH, *et al*. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. *Am J Obstet Gynecol* 1996;**174:**1433–40.

6 Bedford Russell AR, Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? *BJOG* 2006;**113:**758–65.

7 RCOG statement on the ORACLE Children Study. Available at *http://www.rcog.org.uk/index.asp?PageID=2515* (accessed on 13 November 2008).
8 Russell AR, Steer PJ. Antibiotics in preterm labour—the ORACLE speaks. *Lancet* 2008;**372:**1276–8. Epub 2008 Sep 17.

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