

From the Chief Medical Officer
Dr Michael McBride

URGENT COMMUNICATION

HSS(MD)32/2008

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Regional Medicines Information Centre

Dear Colleagues

ORACLE CHILDREN STUDY

This letter gives you information about a report on the Oracle Children Study which will be published online by The Lancet on 18 September. This is a 7 year follow-up study of a randomised controlled trial of the use of erythromycin and/or co-amoxiclav for women presenting in premature labour (with or without ruptured membranes).

The study found a small increase in the number of children reported by their parents as having functional impairment or cerebral palsy, in women in spontaneous preterm labour with intact membranes who received antibiotics. These findings require further study. It is important to note that these women had no evidence of infection and would not routinely be given antibiotics. The mechanism by which this association occurred is unclear, particularly as there was no increase in those with ruptured membranes. Although the risk of cerebral palsy is higher in preterm infants, most babies are born at term with no preterm problems and therefore most cases of cerebral palsy occur in babies born at term.



Department of

**Health, Social Services
and Public Safety**

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Your Ref:

Our Ref: HSS(MD)32/2008

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The results of the study have been considered in conjunction with the Medicines and Healthcare Products Regulatory Agency (MHRA), the Commission on Human Medicines (CHM), medical Royal Colleges and the Royal College of Midwives.

CHM advised that any association between erythromycin in Spontaneous Premature Labour and cerebral palsy was unlikely to be a direct effect of the antibiotic but rather due to a number of factors involved in disruption of the natural history of pre-term labour. They have recommended no change to the licences for erythromycin.

A results leaflet has been sent to women in the study who requested it and is available to all those who took part (www.le.ac.uk/oraclechildren). A helpline is also available for study participants on 0800 085 2411 between 9.30 am and 4.30 pm.

Media reports on the study findings may cause patients to approach you with concerns about taking antibiotics during pregnancy or in labour and about the causes of cerebral palsy.

Key messages

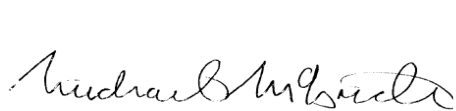
Pregnant women should not feel concerned about taking antibiotics to treat infections. Antibiotics save lives and pregnant women with possible or obvious infections must be considered for treatment with antibiotics.

This study confirms existing good clinical practice that women in spontaneous preterm labour with intact membranes should not routinely be given antibiotics.

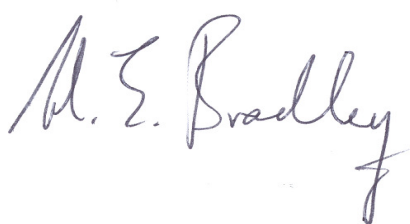
Although the risk of cerebral palsy is higher in preterm infants, most babies are born at term with no preterm problems and therefore most cases of cerebral palsy occur in babies born at term.

This letter also provides some background briefing on the Oracle studies (appendix 1) and Q+As with links to further information resources (appendix 2).

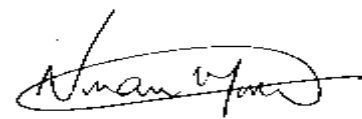
Yours sincerely



Dr Michael McBride
Chief Medical Officer



Mr Martin Bradley
Chief Nursing Officer



Mr Norman Morrow
Chief Pharmaceutical
Officer

Appendix 1

The original ORACLE study

Background

- 1 in 8 babies in the UK is born prematurely
- Prematurity is a major cause of death in the first month after birth

Seven years ago the original ORACLE trial was set up to assess whether premature labour may be linked to underlying maternal infection that could be treated with antibiotics erythromycin and co-amoxiclav. The trial recruited two groups of women: those in premature labour whose waters had broken (spontaneous premature rupture of membranes (PROM)), and those whose waters had not (spontaneous preterm labour and intact membranes (SPL)). There were four treatments being compared and this meant women who agreed to take part were randomly allocated to receive either Erythromycin, or Co-amoxiclav, or both antibiotics, or neither (dummy/placebo pills).

The trial did not include pregnant women showing signs of infection as they should be treated with antibiotics and untreated infections pose serious, potentially life threatening, risks to both mother and baby.

The results of this study, one of the largest ever trials in premature labour, showed that the administration of the antibiotic erythromycin to women whose waters had broken prematurely yielded short-term benefits. These included delaying the onset of labour for the mother and, in the babies, reducing the need for assistance with breathing and reducing infections. The administration of co-amoxiclav in these women increased the risk of necrotising entero-colitis in the babies. The study did not show any benefits or risks to babies born to mothers who had been treated with erythromycin and/or co-amoxiclav whose waters had not broken.

As a result of these findings the RCOG issued guidelines recommending the use of erythromycin for 10 days in women with premature rupture of membranes (PROM). The guidelines did not advocate the use of antibiotics for women in pre-term labour with intact membranes.

http://www.rcog.org.uk/resources/Public/pdf/green_top44_preterm.pdf

What were the results of the ORACLE Children Study?

The ORACLE Children Study, published this week, was designed to look at the progress, seven years later, of the babies born to original trial mothers. It followed up more than 8000 children whose mothers had participated in the initial trial. The results suggest that, despite its short term benefits, erythromycin does not have long term benefits for children whose mothers have preterm rupture of the membranes (PROM.)

For women with spontaneous preterm labour and intact membranes (SPL) the results suggest that there were increases in the numbers of children with functional impairment

who had erythromycin, either on its own or together with co-amoxiclav, (42%) compared with those whose mothers who did not have any erythromycin (38%). These functioning problems included very mild difficulties such as poor co-ordination most of the functioning problems reported by parents were minor. There was no difference in how the children in the two groups did at educational tests (SATs) which primary school children take at the end of key stage 1 of the National Curriculum.

The study also made a very important and unexpected discovery about cerebral palsy. The reporting by parents of cerebral palsy was somewhat more common in the group of women with signs of premature labour and intact membranes who received antibiotics compared with those who had none. In those who had any erythromycin (on its own or together with co-amoxiclav) 3.3% of children had cerebral palsy compared with 1.7% of children whose mothers who did not have erythromycin. In those who had co-amoxiclav (on its own or together with erythromycin), 3.2% of children had cerebral palsy compared with 1.9% of children whose mothers who did not have any co-amoxiclav.

Looking at it in more detail, the increase in the number of children with cerebral palsy was clearest in the group of women who had both antibiotics (co-amoxiclav and erythromycin together). In this group, 4.4% of children had cerebral palsy, though even here the numbers with cerebral palsy remain quite small. In the group of mothers who received placebo 1.6% of children had cerebral palsy.

These results highlight the importance of long term follow-up in perinatal trials and the value of funding such research.

The outcomes measured in the ORACLE Children Study

A postal questionnaire was filled in by the child's parents to find out about the children's health, wellbeing and educational attainment.

Functioning: The questionnaire asked about the child's vision, hearing, speech, walking, dexterity, emotions, pain and aspects of thinking such as learning and remembering. Children were classed by researchers as having a 'functioning' problem if the parents reported that the children had *any* problem or difficulties at all in any of these areas. As a result, 'functioning' problems can range from the child having minor problems (things like wearing glasses, requiring a hearing aid, not always being completely happy or having some difficulty with trying to solve day to day problems) to more severe problems (such as being unable to walk, see, hear or speak, or having severe difficulties with thinking and remembering).

Health problems and behaviour: The questionnaire asked about chest symptoms, hospital admissions, fits/seizures, and specific medical conditions (including cerebral palsy), as well as behaviour, emotions, hyperactivity, and relationships with others.

Educational attainment: The National Curriculum (Key Stage 1) tests for reading, writing and maths, which are undertaken by children aged 7 in England, were used to assess how well children were doing at school.

Appendix 2

Questions & Answers

How was cerebral palsy defined in the study and what is the spectrum of disability observed in the children?

Cerebral palsy is more common in preterm children but the numbers reported by the parents in the treated groups were more than those reported in the untreated group and more than those expected in this group of children. However, the spectrum of disability was the same.

Cerebral palsy is not a disease or an illness. It is the description of a physical impairment that affects movement. The movement problems vary from mild to extremely severe and this was what was found within the Study children. Cerebral palsy is most commonly the result of failure of a part of the brain to develop, either before birth or in early childhood. This is sometimes because of a blocked blood vessel, complications in labour, extreme prematurity or illness just after birth. Infections during pregnancy, or infancy and early childhood, e.g. meningitis or encephalitis, can also cause cerebral palsy. It is usually diagnosed early in life and does not occur for the first time when the child is older.

Many people with cerebral palsy are hardly affected. Others have problems walking, feeding, talking or using their hands. Some people are unable to sit up without support and need constant help. Sometimes other parts of the brain are also affected, causing sight problems, varying degrees of deafness and learning difficulties.

What should clinicians advise the woman with PPROM following these results?

Advice from the RCOG is that the recommendations of its clinical guidelines do not require any changes following publication of the findings of the ORACLE study.

Preterm Prelabour Rupture of Membranes (2006)

http://www.rcog.org.uk/resources/Public/pdf/green_top44_preterm.pdf and *Prevention of Early-Onset Neonatal Group B Streptococcal Disease* (2003)

http://www.rcog.org.uk/resources/Public/pdf/GroupB_strep_no36.pdf.

What should clinicians advise the woman with SPL following these results?

The findings suggest that antibiotics should *not* be given to women who are in spontaneous preterm labour with intact membranes and who do not have an obvious infection.

Should women who have definite infection in pregnancy be treated with antibiotics?

Pregnant women with a possible or obvious infection should continue to be prescribed antibiotics as this may be life-saving for both mother and baby. ***These findings do not mean that antibiotics are unsafe for use in pregnancy.***

What help is being provided for the women involved in the Study

A letter and results leaflet was sent to participants just before publication in The Lancet and a Helpline is in place in the short term to deal with their concerns.

A CMO/CNO cascade which communicates the results to GPs, Maternity units and Community Paediatricians has been sent by the Department of Health so clinicians should have information to address any wider concerns that pregnant or recently delivered mothers may have. All maternity units in UK and those which collaborated abroad have also been sent a summary of the results.

Where should I refer someone with concerns who was part of the Trial?

In the immediate period following the release of the results the helpline is the best place to refer participants on 0800 085 2411

Do these results also apply to other antibiotics?

As the only information we have from this study is on erythromycin and co-amoxiclav, and there are no similar studies on other antibiotics, it is not possible to state whether the results also apply to other antibiotics. However, it is important to note that these results only apply to women who are in spontaneous preterm labour with intact membranes and who do not have an obvious infection. These women would not routinely receive antibiotics. Antibiotics should continue to be used during pregnancy in line with current guidance and the product licence.

Will the product licences for erythromycin be changed?

No. The Commission on Human Medicines, which is responsible for advising on the safety of medicines, has considered the results of the Oracle Children Study in detail. They advised that if the finding was real, it was unlikely to be a direct effect of the antibiotic but rather due to a number of factors involved in disruption of the natural history of preterm labour.

They advised that no regulatory action to amend the licences for erythromycin was appropriate on the basis of the study but that further work should be undertaken to help establish whether this was a chance finding. The Medical Research Council is taking this forward.

Are any mothers still given erythromycin or other antibiotics in cases of premature labour where their membranes have not ruptured and there is no obvious infection? And if so what do you can you advise them?

The use of antibiotics in this situation has never been recommended in national guidelines and it is unlikely that many mothers will have been prescribed them.

It is important to reassure parents that even in the unlikely event that the mother had been prescribed antibiotics in this situation the chance of the child developing any of the problems seen in this study due to the use of the antibiotic is very small.

The very fact of being premature means that these babies already have a higher chance of developing functioning problems in the first place. Child health checks will have already picked up any disabilities that their child might have and these will be being managed.

If a mother wants to find out if she had been prescribed antibiotics then it is necessary to check back with her maternity care providers where these details would be recoded in her notes.

What is the risk (in layman's terms) ?

For premature babies the risk of cerebral palsy is higher than for babies born at full term. The best estimate of the risk for the type of children included in this study is around 2 in every hundred children. The risk in those whose mothers took erythromycin and/or co-amoxiclav was between 3 and 4 in every hundred children

What is cerebral palsy?

Cerebral palsy (cp) is not a disease or an illness. It is the description of a physical impairment that affects movement. The movement problems vary from barely noticeable to extremely severe. No two people with cp are the same; it is as individual as people themselves.

"Cerebral palsy" includes a variety of conditions. The three main types correspond to injuries to different parts of the brain:

- People with *spastic cp* find that some muscles become very stiff and weak, especially under effort. This can affect their control of movement.
- People with *athetoid cp* have some loss of control of their posture, and they tend to make unwanted movements.
- People with *ataxic cp* usually have problems with balance. They may also have shaky hand movements and irregular speech.

What do you mean by 'mild functional impairment'?

Needing to wear glasses or use a hearing aid and problems with day to day problem-solving, these types of things.