Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial

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Lancet 2008; 372: 1310–18

Published Online September 18, 2008 DOI:10.1016/S0140-6736(08)61202-7

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Summary

Background **The ORACLE I trial compared the use of erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) with that of placebo for women with preterm rupture of the membranes without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study—the ORACLE Children Study I—was to determine the long-term effects on children of these interventions.**

Methods **We assessed children at age 7 years born to the 4148 women who had completed the ORACLE I trial and who were eligible for follow-up with a structured parental questionnaire to assess the child's health status. Functional impairment was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from the mark III Multi-Attribute Health Status classification system. Educational outcomes were assessed with national curriculum test results for children resident in England.**

Findings **Outcome was determined for 3298 (75%) eligible children. There was no difference in the proportion of children with any functional impairment after prescription of erythromycin, with or without co-amoxiclav, compared with those born to mothers who received no erythromycin (594 [38·3%] of 1551 children *vs* 655 [40·4%] of 1620; odds ratio 0·91, 95% CI 0·79–1·05) or after prescription of co-amoxiclav, with or without erythromycin, compared with those born to mothers who received no co-amoxiclav (645 [40·6%] of 1587 *vs* 604 [38·1%] of 1584; 1·11, 0·96–1·28). Neither antibiotic had a significant effect on the overall level of behavioural difficulties experienced, on specific medical conditions, or on the proportions of children achieving each level in reading, writing, or mathematics at key stage one.**

Interpretation **The prescription of antibiotics for women with preterm rupture of the membranes seems to have little effect on the health of children at 7 years of age.**

Funding **UK Medical Research Council.**

Introduction

The sequelae of preterm birth pose major public-health challenges. Children born preterm are at risk of major disabilities—eg, cerebral palsy—with risk increasing as length of gestation at birth decreases;[1] many preterm children without disability develop important behavioural and educational difficulties.[2,3] The prevention of preterm birth and reduction of associated disability are therefore important health priorities.

Intrauterine infection and inflammation have been associated with an increased risk of preterm birth[4] and independently with cerebral palsy and chronic lung disease.[5] The antecedent of preterm birth which has been most strongly associated with infection and inflammation is preterm rupture of the fetal membranes (PROM). With conventional microbiological techniques, microbial invasion of the amniotic cavity has been identified in about 30% of cases of PROM;[6] more sensitive PCR techniques that detect conserved 16s rRNA genes suggest that about 70% of births are found to be colonised after PROM.[7]

Against this background, there is unbiased evidence from randomised controlled trials for antibiotic treatment of women with PROM. The ORACLE I trial[8] assessed the use of amoxicillin–clavulanate (co-amoxiclav) 375 mg, or erythromycin 250 mg, or both, or placebo, four times daily for 10 days or until birth (whichever was sooner) in women presenting with PROM using a factorial randomised controlled trial design. In singleton babies born to women after PROM, erythromycin decreased the risk of the composite primary outcome (death or major cerebral abnormality or chronic neonatal lung disease). The prescription of erythromycin was also associated with prolongation of pregnancy and reductions in neonatal morbidity compared with women who did not receive erythromycin, and is now recommended practice.[9] Co-amoxiclav was not associated with any change in the primary endpoint. However, although women who received co-amoxiclav had prolonged pregnancy compared with those who did not receive any co-amoxiclav, it was also associated with a significantly higher incidence of neonatal necrotising enterocolitis.

In this paper we report the results of the ORACLE Children Study I (OCS I), which provided a unique opportunity to determine whether the perinatal use of erythromycin and/or co-amoxiclav for women with

PROM in ORACLE I resulted in differences in functional and educational ability in childhood.

Methods

Participants

OCS I began in 2002 and sought follow-up information for children at 7 years of age who were born to the 4809 women with PROM who completed ORACLE I.[8] The study protocol has been described in detail elsewhere.[10] Briefly, in the original trial, women were informed of the intention to do a subsequent follow-up assessment when they gave written informed consent. Children were traced with the help of the UK Office of National Statistics (ONS) and by contact with their family doctors (general practitioners; GPs). Details of deaths and families who moved out of the UK were notified to us by ONS. We did not attempt to contact the families of children who had been adopted, were in foster care, or had emigrated.

Contact details of surviving children were obtained from the National Health Service (NHS) National Strategic Tracing Service (NSTS). If no response was obtained to an invitation letter, the child's GP was contacted to check details and possible reasons for non-response (eg, the child was currently in care or was a non-English speaker). Translations of all study materials were available. For those children who were not 7 years of age at the initial invitation, contact was maintained from 2001 onwards with birthday cards, newsletters, and change of address cards, and via a website.

When the child was 7 years old we confirmed their current address with ONS and the GP. An information leaflet was sent to the parents, and 2 weeks later the study questionnaire was sent. If no response was obtained, contact details were checked with the GP and a reminder letter, including a £5 high street voucher,[11] was sent by registered post to the parents or carers of the child during the week of the child's 7th birthday. If no response was forthcoming, 3 weeks later, a final letter was sent or telephone contact was made.

The West Midlands Multi-centre Research and Ethics Committee (MREC) 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, both of which met annually. Those involved in tracing and data entry remained blind to the allocated treatment. All data to assess health and educational outcomes were double entered and subject to validation and logic checks.

Data collection

Data were collected with a parent-completion postal questionnaire. This comprised the Health Utilities Index (HUI)[12] from which the Multi-Attribute Health Status (MAHS) is derived, the Strengths and Difficulties Questionnaire,[13] and specific questions on respiratory symptoms,[14] hospital admissions, convulsions, other specific medical conditions, and demographic data.

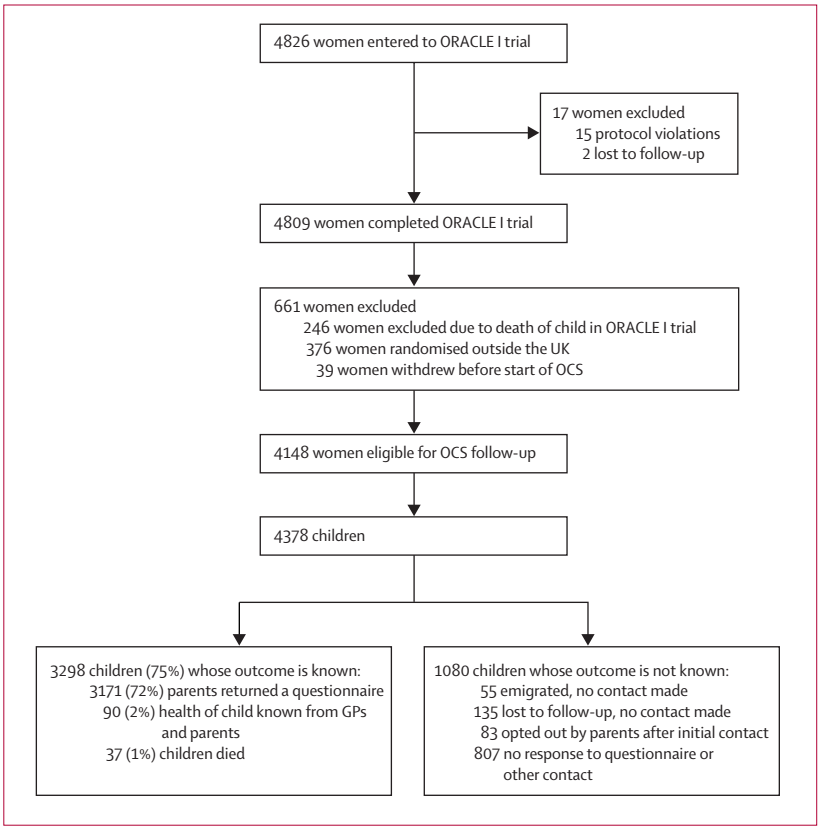

Figure 1: **Flowchart for PROM group through ORACLE I and extended follow-up in OCS I**
*291 babies died during ORACLE I. However, only 246 women were excluded because a number had a multiple birth. Of the 291 babies, 225 were singletons, 42 were twins where both babies died (21 sets), and 24 were multiple births with live siblings.

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[12] within any of the individual attributes of vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute has either five or six defined levels of impairment, ranging from normal function to severe dysfunction.[15] These have been classified further into none, mild, moderate, or severe levels of severity for the individual attributes from the standard algorithms available within the HUI coding/procedure manual. The overall level of functional impairment was determined by their worst score in any attribute. Sensitivity analyses were also done based on the HUI3 multi-attribute utility scores of overall health-related quality of life,[16] which became available after the study had begun.

Secondary outcomes were the presence of three or more abnormal attributes derived from the MAHS classification system and the degree of functional impairment (severe, moderate, mild, none) within the individual domains; the number of deaths between trial entry and discharge and age 7 years; overall and subscale

scores derived from the parent-completed Strengths and Difficulties Questionnaire; the frequency of specific medical conditions including CNS problems (cerebral palsy, fits/seizures, hydrocephalus with a shunt), respiratory problems (wheezing, medication for asthma), hospital admission (both in the last year and for chest problems), diabetes, bowel disorders, and developmental problems (attention deficit hyperactivity disorder derived from the Strengths and Difficulties Questionnaire[17] or parent report), and other development problems.

With support from the UK Qualifications and Curriculum Authority (QCA), we used results from national curriculum tests (key stage one), done at 7 years of age to assess the children's educational attainment for residents in England. Such tests are not routinely done in other parts of the UK. Changes to the way in which the results of these tests are derived have occurred since 2005, when the assessment became teacher-based rather than test-based, with the results of written tests used by the teacher to inform the level awarded.[18]

At key stage one, all children are awarded a level for each of reading, writing, and mathematics. These include levels three and four, which are above average, level two (the average level awarded to 60–70% of pupils, and which is also subdivided into three sublevels), and below level two, which includes children who attained level one, those who were working towards level one, or who were not entered by the teacher. For all eligible OCS I children in England, key stage one level data were provided anonymously by the UK Department for Children, Schools and Families (DCSF), categorised by treatment group.

Statistical analysis

The size of the study was predefined by the number of women recruited to the ORACLE I trial. The indicative power calculation in the protocol noted that about 4400 children were expected to be eligible for the follow-up study. About 3·1% of the children in the any erythromycin group were expected to have three or more abnormal attributes using the MAHS scale.[12] Assuming an 85% response rate, this gave 80% power (with two-tailed α=0·05) to detect a prevalence of three or more abnormal attributes in the no erythromycin group of 5% (a relative difference between the two groups of 38%).

	Erythromycin and co-amoxiclav	Erythromycin	Co-amoxiclav	Placebo
At entry to ORACLE I				
Number of women	737	754	808	775
Maternal age (years)	28·8 (24·2–32·8)	28·4 (23·7–32·6)	28·8 (24·4–32·6)	28·7 (24·4–32·7)
Gestational age (days)	226 (209–238)	225 (205–237)	225 (208–238·5)	226 (205–238)
Multiple births	52 (7·1%)	56 (7·4%)	46 (5·7%)	49 (6·3%)
Maternal antibiotics in the postnatal period	180 (24·4%)	191 (25·3%)	211 (26·1%)	209 (27·0%)
Short-term outcomes of ORACLE I				
Number of babies	783	807	849	822
Birth within 48 h of trial entry	270 (34·5%)	296 (36·7%)	279 (32·9%)	343 (41·7%)
Birth within 7 days of trial entry	442 (56·5%)	516 (63·9%)	498 (58·7%)	539 (65·6%)
Gestational age (days)	237 (222–249)	236 (221–247)	237 (222–248)	236 (221–247)
Birthweight (g)	2120 (1670–2585)	2092 (1611–2490)	2115 (1675–2560)	2075 (1626–2550)
Sex (male)	413 (52·7%)	422 (52·3%)	454 (53·5%)	463 (56·3%)
Admission to neonatal unit	570 (72·8%)	605 (75·0%)	623 (73·4%)	630 (76·6%)
Ventilated	147 (18·8%)	169 (20·9%)	168 (19·8%)	158 (19·2%)
Respiratory distress syndrome	154 (19·7%)	164 (20·3%)	159 (18·7%)	163 (19·8%)
Supplementary oxygen at 28 days	61 (7·8%)	69 (8·6%)	81 (9·5%)	74 (9·0%)
Positive blood culture	44 (5·6%)	39 (4·8%)	48 (5·7%)	57 (6·9%)
Necrotising enterocolitis (suspected or proven)	22 (2·8%)	13 (1·6%)	23 (2·7%)	20 (2·4%)
Abnormal cerebral ultrasonography	26 (3·3%)	26 (3·2%)	20 (2·4%)	27 (3·3%)
At entry to OCS I				
Ethnic origin (white)	710 (90·7%)	743 (92·1%)	757 (89·2%)	748 (91·0%)
Smoking in family	351 (44·8%)	364 (45·1%)	387 (45·6%)	351 (42·7%)
Damp or mould problems	47 (6·0%)	43 (5·3%)	41 (4·8%)	51 (6·2%)
Family history of asthma	354 (45·2%)	368 (45·6%)	346 (40·8%)	353 (42·9%)
Child's age at completion of questionnaire (years)	6·97 (6·91–7·08)	6·97 (6·91–7·07)	6·94 (6·91–7·05)	6·95 (6·91–7·06)
Child's age at the start of the academic year they sat key stage one tests (years)	6·46 (6·25–6·67)	6·50 (6·25–6·75)	6·50 (6·25–6·67)	6·50 (6·25–6·75)

Data are n (%) or median (IQR).

Table 1: **Characteristics of the responders in the PROM group**

	Any erythromycin (N=1551)	No erythromycin (N=1620)	OR (95% CI)	Any co-amoxiclav (N=1587)	No co-amoxiclav (N=1584)	OR (95% CI)
No functional impairment	957 (61·7%)	965 (59·6%)	Ref	942 (59·4%)	980 (61·9%)	Ref
Any functional impairment	594 (38·3%)	655 (40·4%)	0·91 (0·79–1·05)	645 (40·6%)	604 (38·1%)	1·11 (0·96–1·28)
Mild	336 (21·7%)	382 (23·6%)	0·89 (0·75–1·05)	375 (23·6%)	343 (21·7%)	1·14 (0·96–1·35)
Moderate	173 (11·2%)	181 (11·2%)	0·96 (0·77–1·21)	175 (11·0%)	179 (11·3%)	1·02 (0·81–1·28)
Severe	85 (5·5%)	92 (5·7%)	0·93 (0·68–1·27)	95 (6·0%)	82 (5·2%)	1·21 (0·89–1·64)
Three or more abnormal attributes	128 (8·3%)	130 (8·0%)	1·03 (0·80–1·33)	135 (8·5%)	123 (7·8%)	1·10 (0·86–1·42)

Table 2: **Overall level of functional impairment at age 7 years from the mark III Multi-Attribute Health Scale in children whose mothers had PROM**

	Erythromycin and co-amoxiclav (N=763)	OR (95% CI)	Erythromycin only (N=788)	OR (95% CI)	Co-amoxiclav only (N=824)	OR (95% CI)	Double placebo (N=796)	OR (95% CI)
No functional impairment	462 (60·6%)	0·98 (0·80–1·21)	495 (62·8%)	1·08 (0·88–1·33)	480 (58·3%)	0·89 (0·73–1·09)	485 (60·9%)	Ref
Any functional impairment	301 (39·4%)	1·02 (0·83–1·25)	293 (37·2%)	0·92 (0·75–1·13)	344 (41·7%)	1·12 (0·92–1·36)	311 (39·1%)	Ref
Mild	178 (23·3%)	1·01 (0·79–1·29)	158 (20·1%)	0·84 (0·65–1·07)	197 (23·9%)	1·08 (0·85–1·36)	185 (23·2%)	Ref
Moderate	80 (10·5%)	0·98 (0·70–1·36)	93 (11·8%)	1·06 (0·77–1·46)	95 (11·5%)	1·12 (0·81–1·53)	86 (10·8%)	Ref
Severe	43 (5·6%)	1·13 (0·72–1·77)	42 (5·3%)	1·03 (0·66–1·61)	52 (6·3%)	1·31 (0·85–2·02)	40 (5·0%)	Ref
Three or more abnormal attributes	63 (8·3%)	1·15 (0·79–1·66)	65 (8·2%)	1·14 (0·79–1·65)	72 (8·7%)	1·22 (0·85–1·75)	58 (7·3%)	Ref

Odds ratios are comparisons with the double placebo group.

Table 3: **"Inside the table" analysis of overall level of functional impairment at age 7 years from the mark III Multi-Attribute Health Scale in children whose mothers had PROM**

Odds ratios with 95% CI are presented for primary and secondary outcomes in the groups receiving co-amoxiclav (any co-amoxiclav: either with or without erythromycin) and erythromycin (any erythromycin: either with or without co-amoxiclav) separately. Odds ratios approximate relative risks when the risk is low.[19] Logistic models with terms indicating allocation to co-amoxiclav and erythromycin and an interaction term, corresponding to the ORACLE I trial's factorial design, were also fitted.[20] Since our findings were generally not altered when interaction terms were included, for simplicity they have not been included in models presented in the main tables, but they are available on the internet. Multiple births were treated as being independent in the analyses, but sensitivity analyses based on randomly selecting one child were also done.[21]

Data from the Strengths and Difficulties Questionnaire were classified as normal, borderline, or abnormal. Odds ratios and CI for proportions with borderline or abnormal scores are presented. Models with interaction terms were also fitted as above.

Subgroup analyses were done as specified in the protocol, relating to multiple and singleton pregnancies, and gestational age subgroups used at the time of randomisation (<32 weeks' gestation and <28 weeks' gestation).

Relative risks and 95% CI for key stage one educational data were obtained from Poisson regression models, adjusting for test year. Because of restricted information available from the anonymous summary of these data supplied by the DCSF, sensitivity and subgroup analyses were not possible for these data.

Most of the outcomes presented, including the primary outcome of the follow-up study, can only be assessed in surviving children. Thus the analyses presented are not based on the intention-to-treat principle (ie, by analysis of outcomes in all those entered into the trial). However, the absolute risk of death was low, limiting any potential bias that might be introduced by undertaking the analyses of surviving children only, as pre-specified in the study protocol. There were no clear differences in the numbers of deaths in each of the study groups at the end of ORACLE I, but we present sensitivity analyses using a composite death or any functional impairment outcome to confirm the limited effect of including deaths in the analyses.

Informal allowance for the large number of comparisons undertaken is made in interpreting the results throughout.[22]

Outcomes for children not assessed may differ from outcomes for those who were assessed.[23] To explore this, we investigated differences between responders and non-responders for a variety of factors: treatment group, short-term maternal and neonatal outcomes, ethnicity, indices of deprivation from ONS derived from post code, and for those children in England, educational attainment.

For more on **indices of deprivation** see http://www.neighbourhood.statistics.gov.uk

Role of the funding source

The study sponsors had no involvement in the study design; collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication. DJ and KP had full access to all the data. SK had final responsibility for the decision to submit for publication.

Results

Of the 4378 UK children eligible for follow-up, outcome was known for 3298 (75%). Full questionnaire data are available for 3171 (72%) children, data were collected from telephone interview or GP for 90 children (2%; included in the analysis of specific medical conditions); 37 (1%) children had died (figure 1). Women were unaware of their treatment allocation with the exception of one woman who requested this information before returning data for OCS I. Only 0·8% of data within returned questionnaires were missing. Full key stage one educational data were available for 3238 (96%) of the 3377 English children who had been entered into the tests by 2007. The characteristics of the responders, in each factorial group, were broadly similar in terms of maternal, demographic, and neonatal data to that of the main ORACLE I trial results (table 1).

Children whose outcome was unknown had younger mothers and experienced less neonatal morbidity (webtable 1), and, at least for those in England, were from more deprived areas than those whose outcome was known (webtable 2). More English children whose outcome was unknown scored below level two in key stage one tests, and were less likely to be white than were those whose outcome was known (webtable 2).

See Online for webtables 1–7

There was no difference in the proportion of children with any functional impairment whose mothers had been prescribed any erythromycin, compared with those who received no erythromycin, or in the proportion of children with any functional impairment whose mothers had received co-amoxiclav, compared with those who received no co-amoxiclav (table 2). There was no evidence of an effect of either antibiotic on any functional impairment when fitting a logistic model with terms for erythromycin, co-amoxiclav, and an interaction between the antibiotics (webtable 3); this model also showed no evidence for an interaction in effects between the antibiotics (webtable 3). Neither antibiotic had an effect on any functional impairment when missing data were assumed to correspond to a functional impairment (data not shown). Table 3 presents the results for the four treatment groups "inside the table" of the factorial trial;[24] there were no clear differences between the treatment groups. Sensitivity analyses based on the HUI3 multi-attribute utility function[16] showed similar results (webtable 4). The use of erythromycin or of co-amoxiclav was not associated with any change in risk of death or of a composite endpoint of death or any functional impairment (table 4; webtable 5).

Neither antibiotic had a significant effect on the overall level of behavioural difficulties experienced or the impact on families (table 5; webtable 6). Neither antibiotic had any effect on the proportions of children failing to achieve each level in reading, writing, or mathematics at key stage one (table 6). Compared with national data, a higher proportion of the children surveyed here attained a score below level two (table 6).

There were no significant differences with either antibiotic in the proportions of children reported as having

	Any erythromycin	No erythromycin	OR (95% CI)	Any co-amoxiclav	No co-amoxiclav	OR (95% CI)
Number of women	2178	2255		2204	2229	
Number of children	2323	2389		2336	2376	
Stillbirths	42 (1·8%)	44 (1·8%)	0·98 (0·64–1·50)	45 (1·9%)	41 (1·7%)	1·12 (0·73–1·71)
Deaths in first year	107 (4·6%)	124 (5·2%)	0·88 (0·68–1·15)	113 (4·8%)	118 (5·0%)	0·97 (0·75–1·27)
Deaths after first year	7 (0·3%)	4 (0·2%)	1·79 (0·52–6·12)	5 (0·2%)	6 (0·3%)	0·85 (0·26–2·78)
Total deaths	156 (6·7%)	172 (7·2%)	0·93 (0·74–1·16)	163 (7·0%)	165 (6·9%)	1·01 (0·80–1·26)
Total death or any functional impairment	750 (32·3%)	827 (34·6%)	0·90 (0·80–1·02)	808 (34·6%)	769 (32·4%)	1·11 (0·98–1·25)
Total death or three or more abnormal attributes	284 (12·2%)	302 (12·6%)	0·96 (0·81–1·14)	298 (12·8%)	288 (12·1%)	1·06 (0·89–1·26)

Table 4: **Deaths in ORACLE I and during OCS I in children whose mothers had PROM**

	Any erythromycin (N=1551)	No erythromycin (N=1620)	OR (95% CI)	Any co-amoxiclav (N=1587)	No co-amoxiclav (N=1584)	OR (95% CI)
Emotional symptoms	295 (19·0%)	284 (17·5%)	1·10 (0·92–1·32)	290 (18·3%)	289 (18·2%)	1·00 (0·84–1·20)
Conduct problems	398 (25·7%)	433 (26·7%)	0·95 (0·81–1·11)	415 (26·1%)	416 (26·3%)	0·99 (0·85–1·16)
Hyperactivity	372 (24·0%)	443 (27·3%)	0·84 (0·71–0·98)	398 (25·1%)	417 (26·3%)	0·94 (0·80–1·10)
Peer problems	334 (21·5%)	343 (21·2%)	1·02 (0·86–1·21)	350 (22·1%)	327 (20·6%)	1·09 (0·92–1·29)
Prosocial behaviour	98 (6·3%)	131 (8·1%)	0·77 (0·58–1·01)	118 (7·4%)	111 (7·0%)	1·07 (0·81–1·40)
Overall (total difficulties)	310 (20·0%)	340 (21·0%)	0·94 (0·79–1·12)	329 (20·7%)	321 (20·3%)	1·03 (0·87–1·22)
Impact on family	278 (17·9%)	307 (19·0%)	0·93 (0·78–1·12)	298 (18·8%)	287 (18·1%)	1·04 (0·87–1·25)

Data are number of children scoring borderline or abnormal on each scale (%).

Table 5: **Behaviour at age 7 years from the Strengths and Difficulties Questionnaire in children whose mothers had PROM**

CNS or development problems, diabetes, or total bowel disorders (table 7; webtable 7). There is some evidence of a reduction in respiratory problems in the children whose mothers received any erythromycin compared with those who received no erythromycin (table 7). Although there is no evidence of a significant increase in the prevalence of total bowel problems with either antibiotic, more children were reported to have other bowel problems (eg, hospital admission for constipation, diarrhoea, or stomach troubles, or under care of doctor for bowel problems) in the any co-amoxiclav group than in the no co-amoxiclav group (table 7). However, both of these results must be interpreted with caution because of the lack of formal adjustment for multiple comparisons.

Subgroup analyses for multiple/single births and for gestation above and below 28 and 32 weeks were pre-planned; they generally suggest effects consistent with neither antibiotic having an effect on any functional impairment or on the presence of three or more abnormal attributes (figure 2). Adjustment for maternal baseline, social class, and other factors did not substantially alter any of the treatment effects seen here (data not shown). For further analyses, see http://www2.le.ac.uk/Members/drj/supplementary-materials-for-papers.

	Any erythromycin (N=1596)	No erythromycin (N=1642)	RR (95% CI)*	Any co-amoxiclav (N=1623)	No co-amoxiclav (N=1615)	RR (95% CI)*
Reading	360 (22·6%)	363 (22·1%)	1·03 (0·99–1·07)	354 (21·8%)	369 (22·8%)	0·98 (0·94–1·02)
Writing	418 (26·2%)	426 (25·9%)	1·01 (0·97–1·05)	405 (25·0%)	439 (27·2%)	0·98 (0·94–1·01)
Maths	257 (16·1%)	257 (15·7%)	1·01 (0·97–1·06)	250 (15·4%)	264 (16·3%)	0·99 (0·95–1·03)

Data are number of children failing to achieve level two or higher (%). Overall relative risks (RR) and 95% CI are from Poisson models for level achieved adjusting for test year, 2002–07. National norms for 2002–07 have been standardised by the numbers of children in the OCS I cohort each year, and suggest that we would expect the following percentages of children to fail to achieve level two or above: reading 15%, writing 18%, maths 11%. *No evidence of overdispersion when these Poisson models are fitted.

Table 6: **Educational attainment in reading, writing, and mathematics at key stage one, for England only, for children whose mothers had PROM**

	Any erythromycin (N=1590)	No erythromycin (N=1671)	OR (95% CI)	Any co-amoxiclav (N=1632)	No co-amoxiclav (N=1629)	OR (95% CI)
CNS problems						
Cerebral palsy	46 (2·9%)	41 (2·5%)	1·18 (0·77–1·81)	39 (2·4%)	48 (2·9%)	0·81 (0·53–1·24)
Seizures	101 (6·4%)	107 (6·4%)	0·99 (0·75–1·31)	103 (6·3%)	105 (6·4%)	0·98 (0·74–1·29)
On prescribed medication	12 (0·8%)	19 (1·1%)	0·66 (0·32–1·37)	15 (0·9%)	16 (1·0%)	0·94 (0·46–1·90)
Hydrocephalus with shunt	3 (0·2%)	6 (0·4%)	0·52 (0·13–2·10)	6 (0·4%)	3 (0·2%)	2·00 (0·50–8·01)
Developmental problems						
ADHD from SDQ or parental report	109 (6·9%)	135 (8·1%)	0·84 (0·64–1·09)	124 (7·6%)	120 (7·4%)	1·03 (0·80–1·34)
Other developmental problems	6 (0·4%)	11 (0·7%)	0·57 (0·21–1·55)	9 (0·6%)	8 (0·5%)	1·12 (0·43–2·92)
Respiratory problems						
Wheezing in last year	305 (19·2%)	320 (19·2%)	1·00 (0·84–1·19)	309 (18·9%)	316 (19·4%)	0·97 (0·82–1·16)
Medication for chest problems in last year	286 (18·0%)	316 (18·9%)	0·94 (0·79–1·12)	298 (18·3%)	304 (18·7%)	0·97 (0·82–1·16)
Prednisolone	25 (1·6%)	46 (2·8%)	0·56 (0·35–0·92)	42 (2·6%)	29 (1·8%)	1·46 (0·90–2·35)
Oxygen	15 (0·9%)	26 (1·6%)	0·60 (0·32–1·14)	21 (1·3%)	20 (1·2%)	1·05 (0·57–1·94)
Relievers	261 (16·4%)	293 (17·5%)	0·92 (0·77–1·11)	273 (16·9%)	279 (17·1%)	0·98 (0·82–1·18)
Preventers	197 (12·4%)	219 (13·1%)	0·94 (0·76–1·15)	211 (12·9%)	205 (12·6%)	1·03 (0·84–1·27)
Hospital admission						
Admission to hospital in last year	196 (12·3%)	223 (13·3%)	0·91 (0·74–1·12)	211 (12·9%)	208 (12·8%)	1·01 (0·83–1·25)
Admission for chest problems	27 (1·7%)	45 (2·7%)	0·62 (0·39–1·01)	35 (2·1%)	37 (2·3%)	0·94 (0·59–1·50)
Diabetes						
Diabetes	3 (0·2%)	1 (0·1%)	3·16 (0·33–30·38)	4 (0·2%)	0 (0·0%)	..
Bowel disorders						
All bowel problems	61 (3·8%)	57 (3·4%)	1·13 (0·78–1·63)	65 (4·0%)	53 (3·3%)	1·23 (0·85–1·78)
Bowel stoma	23 (1·4%)	25 (1·5%)	0·97 (0·55–1·71)	21 (1·3%)	27 (1·7%)	0·77 (0·44–1·37)
Other bowel problems	38 (2·4%)	32 (1·9%)	1·25 (0·78–2·02)	44 (2·7%)	26 (1·6%)	1·71 (1·05–2·79)

ADHD=attention deficit hyperactivity disorder. SDQ=Strengths and Difficulties Questionnaire.

Table 7: **Medical conditions reported by parents of children at age 7 years whose mothers had PROM**

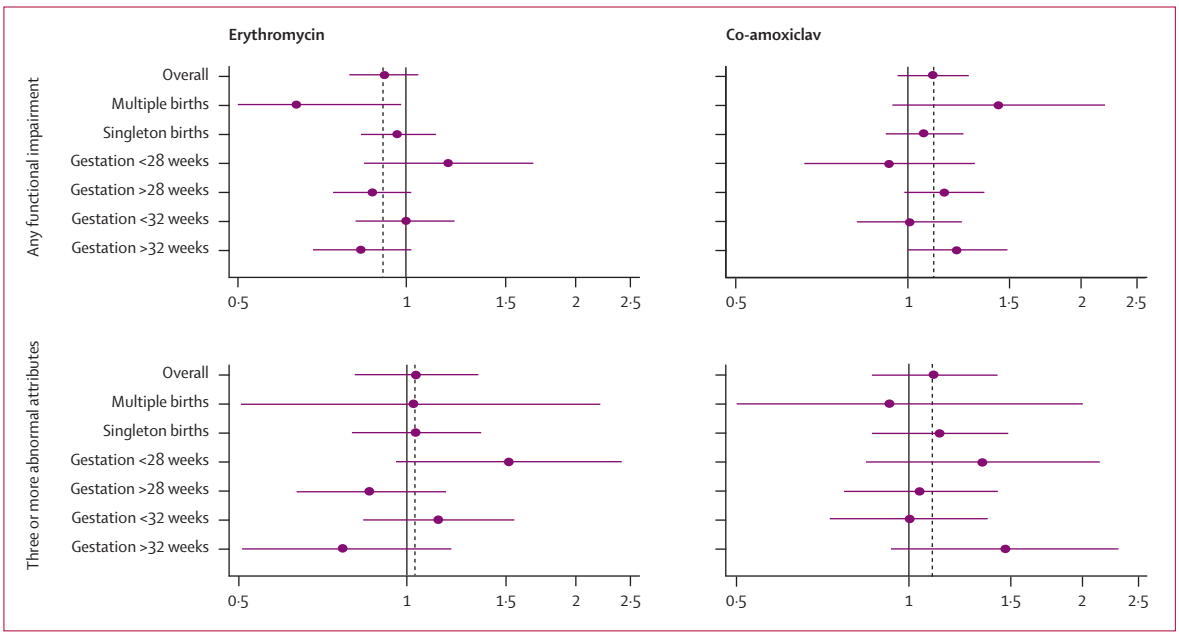

Figure 2: **Subgroup analyses for overall functional impairment for children whose mothers had PROM**

Discussion

In this long-term follow-up of children whose mothers were entered into the ORACLE I trial of antibiotics prescribed for women with PROM and no overt signs of infection, there is no evidence of any substantial long-term effect in children at age 7 years associated with the prescription of either erythromycin or co-amoxiclav. Although there were some apparent differences in a small number of secondary outcomes—eg, improvement in respiratory function with erythromycin and increased bowel disorders with co-amoxiclav—and despite the fact that these changes are biologically plausible and consistent with the short-term outcomes from the ORACLE I trial, they should be viewed with caution because of the large number of comparisons made.

The size of the ORACLE population made direct face-to-face assessment of outcome impracticable and thus we elected to obtain proxy information about the children from parents. This was possible using well validated and standardised parent report tools, namely the Health Utilities Index and the Strengths and Difficulties Questionnaire, to assess health-related quality-of-life and behaviour, respectively. Although these are validated ways of collecting outcome data, using a questionnaire may mean more subtle differences between the treatment groups were missed. Health conditions could only be assessed through parental report, which also leads to the potential for under reporting and some inaccuracy in ascertainment; in general, this might reduce the power to detect any associations present, since almost all the women in the study remained blind to their allocated treatment.

To achieve high follow-up rates using postal questionnaires is difficult. We used evidence-based strategies to optimise the response[25] and developed our own randomised evidence during the conduct of the study to maximise response.[11] We maintained regular contact with the women originally entered into the trial, allowing us to achieve a high follow-up rate of 75%. Nonetheless, disadvantaged groups are over-represented in the non-responders but there was no evidence of differential non-response between the randomised groups. Although this response rate is lower than that assumed in the initial power calculation, the increased prevalence of functional impairment resulted in power being increased overall.

Cognitive impairment is the most common disability associated with preterm birth.[26,27] School performance is affected by a range of disabilities, of which general cognitive function is the most important, although additional deficits of executive function[28] and attention may be contributory in the preterm child.[2] Although we were unable to achieve direct cognitive assessment, we were able to use anonymised results from national curriculum tests, which allowed us to examine the scholastic attainment for virtually the whole population of surviving children in England, which we have used as a proxy for cognitive outcome. While the results showed no treatment differences in the level of performance reached with either antibiotic, this group of children as a whole have educational attainment below national norms, in keeping with the excess of preterm children with poor academic attainment.[2] Level scores are arguably rather weak measures of attainment; the power of these comparisons would have been increased by use of the raw scores for individual tests, but these are not available centrally.

In women with PROM, positive amniotic fluid cultures are found in 32% of cases at the time of presentation[29] and in as many as 75% during subsequent labour.[30] Antibiotics might therefore be expected to improve clinical outcomes in this situation. There is also increasing evidence that, in addition to preterm birth, intrauterine infection is an independent antecedent of other disability, particularly cerebral palsy[31] and chronic lung disease.[32] Prescription of antibiotics for PROM could prevent neurological and respiratory disability by prolonging pregnancy or by reducing inflammation. It is thus disappointing that the findings of decreased neonatal morbidity after receipt of erythromycin in ORACLE I have not translated into long-term benefit detectable within the measures we used. The reasons for this are not clear but might be linked to the length of antibiotic exposure, which in this group of women was fairly short, since about 60% gave birth within a week.[8] There is also some evidence that antibiotic administration to women with PROM may neither eradicate nor prevent intra-amniotic infection. In a recent study of 18 women with intra-amniotic infection following PROM, only three showed no evidence of infection or inflammation after combination antibiotic treatment for 7–14 days and nine of 28 women with no evidence of intra-amniotic inflammation at admission developed inflammatory changes despite therapy; five of these nine women developed positive amniotic fluid cultures.[33] This evidence suggests that other strategies are necessary to prevent the progress of infection and inflammatory changes in utero in the presence of ruptured membranes.

In the accompanying paper reporting the results of the ORACLE Children Study II[34] in the presence of spontaneous preterm labour with intact membranes, we have observed an increase in the risk of any functional impairment with the use of erythromycin (with or without co-amoxiclav) and, particularly, increases in the numbers of children with cerebral palsy associated with the use of both erythromycin and co-amoxiclav. These results would suggest further caution should be used when considering the routine treatment of women with antibiotics where there is uncertainty about the diagnosis of PROM. It is clear that we need to better understand the role of infection in women with PROM and the role and wider effects of antibiotics in the perinatal period. However, it is important to clarify that the women in ORACLE I with PROM were entered into the trial when there was clinical uncertainty about the need to prescribe antibiotics—ie, they showed no overt clinical signs of maternal or fetal infection. It is critical that women with evidence of clinical infection are treated with antibiotics, since clinical chorioamnionitis remains an important cause of maternal, fetal, and neonatal death. The results of this study should not lead to fewer women with overt signs of maternal or fetal infection receiving treatment.

Contributors

All authors contributed to the study design, developed the protocol, and contributed to drafting the paper. SK led the study and together with DJT and PB contributed knowledge of maternity practice. KP and DRJ provided statistical knowledge; NM and AS contributed knowledge on childhood outcomes.

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Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This study was funded by the UK Medical Research Council and sponsored by University Hospitals of Leicester and approved by their research and development directorate. We thank all the women and children who took part in the study and the obstetricians and midwives who recruited them to the original ORACLE trials. We thank the Office of National Statistics, the NHS National Strategic Tracing Service, and the Data Services Group within the Department of Children, Schools and Families. We also thank the key stage one group (Maggie McLean, John Crookes, Peter Tymms, and Tony Cline) for helpful comments on educational aspects. We thank Steve Gould, Barbara Farrell, Phil Edwards, and Martin Rosser for advice on questionnaire design. We convened a group of experts from within the field to help us understand and interpret these finding before publication. This group consisted of Martin Whittle, Alison Bedford Russell, Phil Bennett, Kate Costeloe, Francis Cowan, Olaf Dammann, Diana Elbourne, Catherine Elliott, Mike Millar, Jane Norman, Micheal O'Shea, Max Parmar, Roberto Romero, and Dieter Wolke.

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