Articles

Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial

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Summary

Background Preterm, prelabour rupture of the fetal membranes (pPROM) is the commonest antecedent of preterm birth, and can lead to death, neonatal disease, and long-term disability. Previous small trials of antibiotics for pPROM suggested some health benefits for the neonate, but the results were inconclusive. We did a randomised multicentre trial to try to resolve this issue.

Methods 4826 women with pPROM were randomly assigned 250 mg erythromycin (n=1197), 325 mg co-amoxiclav (250 mg amoxicillin plus 125 mg clavulanic acid; n=1212), both (n=1192), or placebo (n=1225) four times daily for 10 days or until delivery. The primary outcome measure was a composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography before discharge from hospital. Analysis was by intention to treat.

Findings Two women were lost to follow-up, and there were 15 protocol violations. Among all 2415 infants born to women allocated erythromycin only or placebo, fewer had the primary composite outcome in the erythromycin group (151 of 1190 [12·7%] *vs* 186 of 1225 [15·2%], p=0·08) than in the placebo group. Among the 2260 singletons in this comparison, significantly fewer had the composite primary outcome in the erythromycin group (125 of 1111 [11·2%] *vs* 166 of 1149 [14·4%], p=0·02). Co-amoxiclav only and co-amoxiclav plus erythromycin had no benefit over placebo with regard to this outcome in all infants or in singletons only. Use of erythromycin was also associated with prolongation of pregnancy, reductions in neonatal treatment with surfactant, decreases in oxygen dependence at 28 days of age and older, fewer major cerebral abnormalities on ultrasonography before discharge, and fewer positive blood cultures. Although co-amoxiclav only and co-amoxiclav plus erythromycin were associated with prolongation of pregnancy, they were also associated with a significantly higher rate of neonatal necrotising enterocolitis.

Interpretation Erythromycin for women with pPROM is associated with a range of health benefits for the neonate, and thus a probable reduction in childhood disability. However, co-amoxiclav cannot be routinely recommended for pPROM because of its association with neonatal necrotising enterocolitis. A follow-up study of childhood development and disability after pPROM is planned.

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Introduction

Preterm, prelabour rupture of the fetal membranes (pPROM) occurs in 2·0–3·5% of pregnancies and is the commonest antecedent of preterm birth, being present in 30–40% of cases.[1] Although the latency period between fetal-membrane rupture and birth varies with gestation, spontaneous labour and birth is a consequence and can result in the complications of prematurity—ie, death; short-term neonatal disease and long-term disability (including cerebral palsy, blindness, and deafness); the complications of infection including chorioamnioitis, maternal wound infection, and neonatal sepsis; and the complications of prolonged oligohydramnios including pulmonary hypoplasia, pneumothorax, and skeletal deformities.[1]

Usually, fetal-membrane rupture is preceded by structural weakness associated with extracellular-matrix degradation and cellular apoptosis,[2,3] but a substantial proportion of cases are associated with subclinical chorioamnionitis.[4] Micro-organisms are believed to degrade the fetal membranes either directly through proteases or phospholipases, or indirectly by the activation of collagenases—members of the matrix metalloproteinase family.[5] Evidence for the role of subclinical chorioamnionitis in pPROM comes from case-control and cohort studies that have shown that women with pPROM have a higher rate of abnormal microbial colonisation of the lower genital tracts than women who have normal births, and from microbiological studies of amniotic fluid taken by amniocentesis from women with pPROM. From published studies, the overall prevalence of positive amniotic-fluid cultures in such women is 32–35%.[4]

Administration of antibiotics to the mother could therefore improve neonatal health and long-term child health by preventing infectious morbidity in the fetus, or by delaying the progression to preterm birth. The most recent Cochrane review of trials of antibiotics in pPROM[6] reported that antibiotics seem to be of benefit in the reduction of the rate of maternal infection, delay of delivery, reduction of the rate of neonatal infection, and reduction of the numbers of babies requiring neonatal intensive care and ventilation for more than 28 days. However, the review did not show evidence of benefit for necrotising enterocolitis, major cerebral abnormality, respiratory distress syndrome, or death (either stillbirth or neonatal death).

We aimed to resolve the issue of whether the effects of antibiotics on neonatal outcomes are variable or whether they are the consequence of biases associated with small trials. Additionally, we aimed to test whether the beneficial effects reported are related to the antibiotic type used.[7] Observational evidence has implicated a wide range of organisms in the genesis of pPROM. When deciding which antibiotics to test, we considered amoxicillin, co-amoxiclav (amoxicillin/clavulanic acid), clindamycin,

erythromycin, metronidazole, and tetracycline. Tetracycline would have been the antibiotic of choice, but it is contraindicated in pregnancy because of damage to fetal bones and teeth.[8] Co-amoxiclav and erythromycin have the broadest spectrum, the best complementary range of activities, and provided the opportunity to test a β-lactam and a macrolide antibiotic.

Participants and methods

Participants

Pregnant women were eligible if their fetuses were at less than 37 weeks of gestation, if pPROM was present, and if the need to prescribe antibiotics was uncertain. These pragmatic entry criteria were designed to reflect normal clinical practice. Women were excluded if antibiotics were already being prescribed, or if they were thought to be needed for infection. Exclusions also included the usual reasons for which a clinician would not give antibiotics—ie, immediate delivery desirable or unstoppable; fetus not premature enough to cause concern; and contraindications such as allergy, jaundice, and use of theophylline, carbamazepine, digoxin, disopyramide, terfenadine, or astemizole (all of which are contraindicated with erythromycin).

The trial was approved by the local research ethics committees of all 161 participating centres. Women gave written informed consent.

Methods

Women were randomly assigned to one of four possible treatments: 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid) plus 250 mg erythromycin; co-amoxiclav plus erythromycin placebo; erythromycin plus co-amoxiclav placebo; or co-amoxiclav placebo plus erythromycin placebo. Trial medicines were to be taken orally, four times daily, for 10 days or until delivery.

Each woman was assigned a sequentially numbered study-drug pack. The packs contained entry forms, outcome forms, and the study drugs, which were identical in appearance and weight. An independent clinical-supplies company (DHP, Abergavenny, UK) did quality-control checks throughout the packing process, and 284 (2%) packs were randomly selected and analysed externally (Nova Laboratories) and confirmed to contain the allocated medicines. Allocation to the four possible treatments was by computer, with randomly selected blocks of four. Sequential use of the study-drug packs was monitored by quarterly checks of pack use in each collaborating centre. Over the duration of this trial and a concurrent trial (see page 991),[9] 14 272 packs were produced. There were 461 (3·2%) missing or void packs. Void packs were those opened by clinicians to randomise, and the women did not give consent.

After randomisation, data were collected on all women, irrespective of whether trial medicines were actually dispensed or taken. For the purposes of analysis, women remained in the treatment group to which they were allocated (ie, intention-to-treat analyses are reported). The unmasking codes were held at the Pharmacy Department, Leicester Royal Infirmary, UK. Study treatment was not revealed, even after delivery, unless there was a clear medical reason for doing so. The trial medicines were revealed in 11 cases during treatment (in nine cases the clinicians were made aware, and in two the women alone were informed); in all cases the trial staff remained unaware of treatment assignment. The data on these women have been included in the analysis.

If a serious adverse event that could have been related to the study medicines was suspected, the trial office was contacted. A serious adverse event was defined as being fatal or life-threatening, disabling or incapacitating, requiring a lengthy hospital stay, resulting in congenital abnormality or cancer, or irreversible.

Three single-sided forms were completed at entry, at discharge of the mother after delivery, and at death or discharge of the baby if he or she was admitted to a neonatal intensive-care unit or a special-care baby unit. Incomplete and inconsistent data were checked at source and corrected. Data were managed according to UK Medical Research Council guidelines for good clinical practice in trials.[10] The trial was registered under the Data Protection Act at The University of Leicester. The UK data set was 100% complete and overall the data set was 99·9% complete. All data were entered and verified by two people on two separate occasions. A random sample of paediatric data (10%) were checked against source documentation. The data were accurate to within acceptable ranges (ie, 0–2·0% error). These checks were done independently of the person completing the forms and the person entering the data.

Further information, including necropsy reports when appropriate, was collected on the babies who died. Death was classified by use of an amended Wigglesworth classification.[11] All deaths were classified independently by the trial director and the trial paediatrician, who were both unaware of treatment allocation. An internal audit was done by the trial coordinator, and a randomly selected sample of 10% was verified by S Gould (Chairman of the UK Confidential Enquiry into Stillbirth and Death in Infancy Death Classification Committee). The infant deaths will be the subject of another publication.

Some characteristics of the women enrolled were collected: maternal age, gestational age at randomisation, cervical dilatation, and drugs prescribed (β-agonists, corticosteroids, indomethacin, nifedipine, others). No data about past obstetric history and other fetal or maternal disease were collected.

We used a composite primary outcome measure of death before discharge from hospital; or major adverse outcome in the baby before discharge—ie, chronic lung disease (defined as receiving daily supplementary oxygen at age 36 weeks post conception); or major cerebral abnormality on ultrasonography before discharge.

The secondary outcome measures were: delivery within 48 h and delivery within 7 days; mode of delivery; number of days in hospital; maternal antibiotic prescription after delivery and before discharge (total and within 14 days of randomisation); neonate's gestational age at delivery (days); birthweight less than 2500 g or less than 1500 g; admission to neonatal intensive-care unit or special-care baby unit; total number of babies ventilated; total number of babies in more than 21% oxygen at 48 h, 7 days, 14 days, and 28 days of age; respiratory distress syndrome confirmed by chest radiograph; treatment with exogenous surfactant; oxygen dependence at more than 28 days of age; positive blood culture indicative of clinical infection (total and within 14 days of randomisation); and necrotising enterocolitis suspected or proven (by radiograph or surgery).

The endpoint for data collection was discharge from hospital. If more than one outcome was found in a multiple pregnancy, the worst outcome was used in the analysis.

Statistical analysis

Differences in categorical outcomes between erythromycin only and placebo only, co-amoxiclav only and

placebo only, any erythromycin and no erythromycin, and any co-amoxiclav and no co-amoxiclav were tested for significance by use of the *Z* test; two-sided p-values are cited throughout. Differences in outcome between erythromycin plus co-amoxiclav and placebo, and between any antibiotic (erythomycin alone, co-amoxiclav alone, or both erythromycin and co-amoxiclav) and placebo (3/1 ratio) were also tested for significance. Differences between outcomes measured as continuous variables were tested for significance by use of an unpaired *t* test if normally distributed, and the Mann-Whitney test otherwise. The protocol specified that subsidiary analyses would be done on women randomised at less than 32 weeks of gestation and at greater than 32 weeks of gestation.

The independent data-monitoring committee looked at the results of interim analyses done by the trial statistician on four occasions. The committee was to report to the trial director and steering committee if the randomised comparisons in the study had provided proof beyond reasonable doubt of a difference in a major endpoint between the study and the control groups, and evidence that would be expected to alter substantially the choice of treatment for patients whose doctors are uncertain about whether to recommend antibiotics. Exact criteria for "proof beyond reasonable doubt" were not specified, but members of the committee agreed that it should involve a difference of at least 3 SD in a major outcome. By this criterion, the exact number of interim analyses were not prespecified. The steering committee, collaborators, and administrators (except those who produced the confidential analysis) remained ignorant of the interim results.

Results

Participants

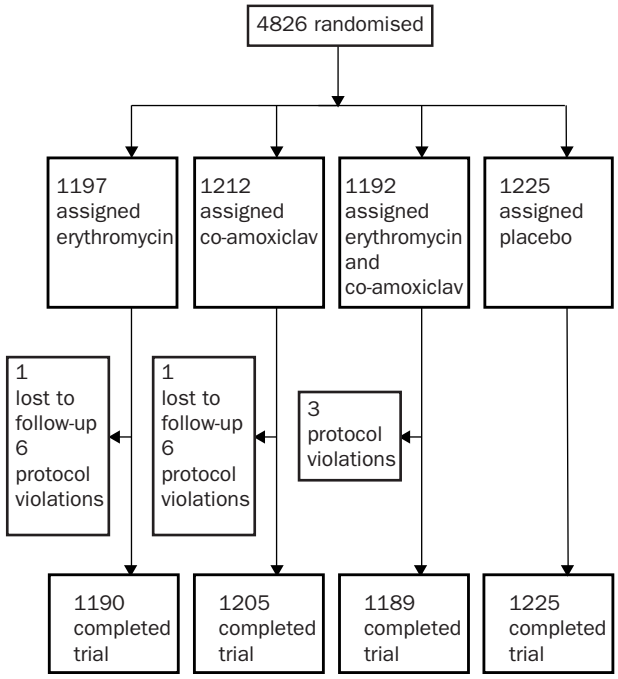
Enrolment was from July 1, 1994, until May 31, 2000. 4826 women with pPROM were randomised—4447 within the UK and 379 from the international collaborating centres. Two women were lost to follow-up and there were 15 protocol violations: four women were enrolled in error or were over 37 weeks' gestation, and 11 were taking contraindicated drugs. 4809 women completed the trial and were analysed (figure). 12 adverse events were reported to the trial director and trial coordinator, and were discussed by the data monitoring committee. None was found to be serious.

Baseline characteristics between the treatment groups were similar (table 1). Median gestation at entry was about 223 days (32 weeks). On recruitment, cervical dilatation was unknown in 46% of women. This situation is typical of clinical practice, in which there is a reluctance to undertake digital vaginal examination because of the known risk of introducing infection. Most women (76·5%) received corticosteroids to mature the fetal lungs. However, use of β-agonists to arrest labour was not as common (8·4%).

Erythromycin

Significantly fewer women on erythromycin alone delivered within 48 h than did those on placebo, and more women on any erythromycin had prolongation of pregnancy for 7 days than women on no erythromycin. There was no evidence of effect on the mode of delivery, or on the number of days spent in hospital. There was a non-significant lower rate of total antibiotic prescription and antibiotic prescription within 14 days of randomisation to women assigned erythromycin (table 2).

The median birthweight was about the same for women who were or were not assigned erythromycin, and there



Trial profile

was no significant difference in number of low birthweight babies (<2500 g), very low birthweight babies (<1500 g), or admissions to neonatal intensive or special care (table 3). In the erythromycin groups, there were fewer babies in more than 21% oxygen at 48 h, 7 days, 14 days, and 28 days of age. In the erythromycin only group compared with the placebo group, this difference was significant in babies requiring supplementary oxygen at any time and at 48 h of age. There were no significant differences in respiratory-distress syndrome, oxygen dependency at more than 28 days of age, babies requiring oxygen at 36 weeks post conception, and positive blood culture. The need for treatment with exogenous surfactant was lower with erythromycin only than with placebo (table 3).

No significant differences between the groups were detected in the number of babies with suspected or proven

	Erythromycin only (n=1190)	Co-amoxiclav only (n=1205)	Erythromycin and co-amoxi-clav (n=1189)	Placebo only (n=1225)
Mean (SD) age years	27·5 (6·1)	28·0 (6·0)	27·8 (6·1)	27·9 (6·1)
Gestational age at entry				
Median (range) gestation (days)	223 (109–258)	223 (136–258)	224 (119–258)	222 (128–258)
<26 weeks	121 (10·2%)	127 (10·5%)	139 (11·7%)	136 (11·1%)
26–28 weeks	186 (15·6%)	173 (14·4%)	162 (13·6%)	195 (15·9%)
29–31 weeks	303 (25·5%)	317 (26·3%)	290 (24·4%)	302 (24·7%)
32–36 weeks	580 (48·7%)	588 (48·8%)	598 (50·3%)	592 (48·3%)
Cervical dilatation (cm)				
Unknown	527 (44·2%)	557 (46·2%)	540 (45·4%)	574 (46·9%)
0–1	565 (47·5%)	544 (45·1%)	561 (47·2%)	536 (43·8%)
>1–2	79 (6·6%)	65 (5·4%)	55 (4·6%)	75 (6·1%)
>2	19 (1·6%)	39 (3·2%)	33 (2·8%)	40 (3·3%)
Drugs prescribed				
β agonists	114 (9·6%)	86 (7·1%)	103 (8·7%)	101 (8·2%)
Steroids	908 (76·3%)	916 (76·0%)	920 (77·4%)	936 (76·4%)
Indomethacin	19 (1·6%)	21 (1·7%)	18 (1·5%)	27 (2·2%)
Nifedipine	17 (1·4%)	30 (2·5%)	22 (1·8%)	34 (2·8%)
Others	70 (5·9%)	72 (6·0%)	70 (5·9%)	67 (5·5%)

Table 1: **Baseline characteristics**

	Erythromycin only (n=1190)	Placebo only (n=1225)	p	Any erythromycin (n=2379)	No erythromycin (n=2430)	p
Delivery within 48 h	414 (34·8%)	498 (40·7%)	0·004	786 (33·0%)	865 (35·6%)	0·062
Delivery within 7 days	725 (60·9%)	775 (63·3%)	0·23	1372 (57·7%)	1470 (60·5%)	0·05
Gestational age at delivery						
Median (range) gestation (days)	236 (150–300)	236 (142–293)	. .	237 (129–300)	236 (142–300)	. .
<37 weeks	1006 (84·5%)	1041 (85·0%)	0·76	2024 (85·1%)	2066 (85·0%)	0·95
<26 weeks	48 (4·0%)	59 (4·8%)	. .	101 (4·2%)	107 (4·4%)	. .
26–28[e] weeks	92 (7·7%)	113 (9·2%)	. .	189 (7·9%)	220 (9·1%)	. .
29–31[e] weeks	220 (18·5%)	231 (18·9%)	. .	425 (17·9%)	446 (18·4%)	. .
32–36[e] weeks	646 (54·3%)	638 (52·1%)	0·39	1309 (55·0%)	1293 (53·2%)	0·44
Mode of delivery						
Spontaneous vaginal	733 (61·6%)	746 (60·9%)	. .	1485 (62·4%)	1501 (61·8%)	. .
Forceps/Ventouse	71 (6·0%)	72 (5·9%)	. .	143 (6·0%)	127 (5·2%)	. .
Vaginal breech	51 (4·3%)	50 (4·1%)	. .	109 (4·6%)	113 (4·7%)	. .
Caesarean section	335 (28·2%)	357 (29·1%)	0·96	642 (27·0%)	689 (28·4%)	0·53
Median (range) days in hospital	4 (0–38)	4 (0–61)	0·80	4 (0–44)	4 (0–183)	0·68
Maternal antibiotic prescription	293 (24·6%)	330 (26·9%)	0·19	586 (24·6%)	640 (26·3%)	0·17
Maternal antibiotic prescription within 14 days	241 (20·3%)	262 (21·4%)	0·49	447 (18·8%)	501 (20·6%)	0·11

[e]Number of days.

Table 2: **Maternal outcomes of women with pPROM randomly assigned erythromycin**

necrotising enterocolitis, in the number of babies with an abnormal cerebral ultrasound scan before discharge from hospital, or in the numbers of deaths. Fewer babies whose mothers were assigned erythromycin had the composite primary outcome (death, chronic lung disease, or major abnormality on cerebral ultrasonography) than those whose mothers were assigned placebo, but this finding was not significant (table 3).

The number of women with a multiple pregnancy assigned to each group were as follows: erythromycin only 79, placebo only 76, any erythromyin 156, and no erythromycin 142. No significant differences were detected for any outcome. When the singleton pregnancies were analysed separately, similar differences to those detected in the main analysis were seen in respect of birthweight, admission to neonatal intensive or special care, ventilation, receipt of oxygen, and respiratory distress syndrome. There were significant differences between the erythromycin only group and the placebo group with regard to treatment with exogenous surfactant (142 [12·8%] *vs* 187 [16·3%], p=0·02), oxygen dependence at 28 days of age or older (77 [6·9%] *vs* 102 [8·9%], p=0·03), positive blood culture (59 [5·3%] *vs* 85 [7·4%], p=0·04), abnormal cerebral ultrasonography (33 [3·0%] *vs* 53 [4·6%], p=0·04), and the composite primary outcome (125 [11·2%] *vs* 166 [14·4%], p=0·02). Similarly, there were significant differences between the group whose mothers were assigned any erythromycin and those whose mothers were assigned no erythromycin with respect to treatment with exogenous surfactant (284 [12·8%] *vs* 346 [15·1%], p=0·02), oxygen dependence at 28 days of age or older (156 [7·0%] *vs* 197 [8·6%],

	Erythromycin only (n=1190)	Placebo only (n=1225)	p	Any erythromycin (n=2397)	No erythromycin (n=2430)	p
Birthweight (g)						
Mean (SD)	2102 (766)	2072 (769)	0·32	2112 (768)	2078 (762)	0·12
Median (range)	2070 (440–4420)	2055 (240–4366)	. .	2090 (180–4710)	2055 (230–4488)	. .
<2500	863 (72·5%)	880 (71·8%)	0·70	1704 (71·6%)	1757 (72·3%)	0·60
<1500	255 (21·4%)	284 (23·2%)	0·30	505 (21·2%)	555 (22·8%)	0·18
Admission to NICU/SCBU	836 (70·3%)	880 (71·8%)	0·39	1654 (69·5%)	1728 (71·1%)	0·23
Total babies ventilated	251 (21·1%)	283 (23·1%)	0·23	495 (20·8%)	537 (22·1%)	0·28
Total babies in >21% O_2	370 (31·1%)	436 (35·6%)	0·02	742 (31·2%)	819 (33·7%)	0·06
At 48 h	302 (25·4%)	358 (29·2%)	0·03	607 (25·5%)	674 (27·7%)	0·08
At 7 days	153 (12·9%)	181 (14·8%)	0·17	311 (13·1%)	349 (14·4%)	0·19
At 14 days	119 (10·0%)	140 (11·4%)	0·26	233 (9·8%)	275 (11·3%)	0·09
At 28 days	95 (8·0%)	116 (9·5%)	0·20	192 (8·1%)	228 (9·4%)	0·11
RDS confirmed by radiography	236 (19·8%)	266 (21·7%)	0·25	478 (20·1%)	507 (20·9%)	0·51
Treatment with exogenous surfactant	176 (14·8%)	217 (17·7%)	0·05	344 (14·4%)	399 (16·4%)	0·06
O_2 dependence >28 days	94 (7·9%)	114 (9·3%)	0·22	188 (7·9%)	225 (9·3%)	0·09
O_2 at 36 weeks post conception	66 (5·5%)	76 (6·2%)	0·49	133 (5·6%)	145 (6·0%)	0·58
Positive blood culture						
Overall	68 (5·7%)	100 (8·2%)	0·02	151 (6·3%)	182 (7·5%)	0·12
If born within 14 days	61 (5·1%)	85 (6·9%)	0·06	119 (5·0%)	148 (6·1%)	0·10
Necrotising enterocolitis						
Suspected or proven	25 (2·1%)	33 (2·7%)	0·34	67 (2·8%)	83 (3·4%)	0·23
Proven	11 (0·9%)	6 (0·5%)	0·20	31 (1·3%)	30 (1·2%)	0·83
Abnormal cerebral ultrasonography	50 (4·2%)	61 (5·0%)	0·36	96 (4·0%)	107 (4·4%)	0·53
Deaths	70 (5·9%)	82 (6·7%)	0·41	147 (6·2%)	161 (6·6%)	0·53
Composite primary outcome	151 (12·7%)	186 (15·2%)	0·08	318 (13·4%)	349 (14·4%)	0·32

NICU=neonatal invensive-care unit; SCBU=special-care baby unit; RDS=respiratory distress syndrome.

Table 3: **Neonatal outcomes of babies born to women with pPROM randomly assigned erythromycin**

	Co-amoxiclav only (n=1205)	Placebo only (n=1225)	p	Any co-amoxiclav (n=2394)	No co-amoxiclav (n=2415)	p
Delivery within 48 h	367 (30·5%)	498 (40·7%)	<0·0001	739 (30·9%)	912 (37·8%)	<0·0001
Delivery within 7 days	695 (57·7%)	775 (63·3%)	0·005	1342 (56·1%)	1500 (62·1%)	<0·0001
Gestational age at delivery						
Median (range) gestation (days)	236 (149–307)	236 (142–293)	. .	237 (129–307)	236 (142–300)	. .
<37 weeks	1025 (85·1%)	1041 (85·0%)	0·95	2043 (85·3%)	2047 (84·8%)	0·58
<26 weeks	48 (4·0%)	59 (4·8%)	. .	101 (4·2%)	107 (4·4%)	. .
26–28[6] weeks	107 (8·9%)	113 (9·2%)	. .	204 (8·5%)	205 (8·5%)	. .
29–31[6] weeks	215 (17·8%)	231 (18·9%)	. .	420 (17·5%)	451 (18·7%)	. .
32–36[6] weeks	655 (54·4%)	638 (52·1%)	0·58	1318 (55·1%)	1284 (53·2%)	0·63
Mode of delivery						
Spontaneous vaginal	755 (62·7%)	746 (60·9%)	. .	1507 (62·9%)	1479 (61·2%)	. .
Forceps/Ventouse	55 (4·6%)	72 (5·9%)	. .	127 (5·3%)	143 (5·9%)	. .
Vaginal breech	63 (5·2%)	50 (4·1%)	. .	121 (5·1%)	101 (4·2%)	. .
Caesarean section	332 (27·6%)	357 (29·1%)	0·21	639 (26·7%)	692 (28·7%)	0·17
Median (range) days in hospital	4 (0–183)	4 (0–61)	0·22	3 (0–183)	4 (0–61)	0·08
Maternal antibiobic prescription	310 (25·7%)	330 (26·9%)	0·5	602 (25·1%)	623 (25·8%)	0·63
Maternal antibiotic prescription within 14 days	239 (19·8%)	262 (21·4%)	0·34	445 (18·6%)	503 (20·8%)	0·05

[6]Number of days.

Table 4: **Maternal outcomes of women with pPROM randomly assigned co-amoxiclav**

p=0·05), and positive blood culture (124 [5·6%] *vs* 162 [7·1%], p=0·04).

Co-amoxiclav

Significantly fewer women assigned any co-amoxiclav than assigned no co-amoxiclav delivered within 48 h and within 7 days. There were no detected differences in mode of delivery or number of days in hospital (table 4). With any co-amoxiclav, compared with no co-amoxiclav, there was a significantly lower rate of maternal antibiotic prescription if delivery occurred within 14 days. This effect was dominated by a significantly lower rate of uterine infection (76 [6·3%] *vs* 103 [8·4%], p=0·05) with co-amoxiclav only, and (136 [5·7%] *vs* 190 [7·9%], p=0·003) with any co-amoxiclav.

The use of any co-amoxiclav was not associated with differences in birthweight, admissions to intensive or special care, or the total number of babies ventilated, compared with use of no co-amoxiclav (table 5). There were significantly fewer babies on more than 21% oxygen in the co-amoxiclav only group than in the placebo group, and fewer at 48 h and 7 days (non-significant). There were no significant differences between the groups with regard to the number of babies with respiratory distress syndrome confirmed by chest radiography or the number of babies receiving exogenous surfactant. No significant differences could be detected in the markers of chronic lung disease (oxygen dependence at 28 days and above or receipt of oxygen at 36 weeks post conception), or in positive blood culture (table 5).

There was a significantly greater number of babies with suspected or proven necrotising enterocolitis in the any co-amoxiclav group than in the no co-amoxiclav group.

	Co-amoxiclav only (n=1205)	Placebo only (n=1225)	p	Any co-amoxiclav (n=2394)	No co-amoxiclav (n=2415)	p
Birthweight (g)						
Mean (SD)	2083 (755)	2072 (769)	0·69	2103 (763)	2087 (769)	0·47
Median (range)	2060 (180–4710)	2055 (240–4366)	. .	2080 (180–4710)	2060 (240–4420)	. .
<2500	877 (72·8%)	880 (71·8%)	0·60	1718 (71·8%)	1743 (72·2%)	0·75
<1500	271 (22·5%)	284 (23·2%)	0·68	521 (21·8%)	539 (22·3%)	0·64
Admission to NICU/SCBU	848 (70·4%)	880 (71·8%)	0·42	1666 (69·6%)	1716 (71·1%)	0·27
Total babies ventilated	254 (21·1%)	283 (23·1%)	0·23	498 (20·8%)	534 (22·1%)	0·27
Total babies in >21% O_2	383 (30·1%)	436 (35·6%)	0·05	755 (31·5%)	806 (33·4%)	0·17
At 48 h	316 (26·2%)	358 (29·2%)	0·1	621 (25·9%)	660 (27·3%)	0·27
At 7 days	168 (13·9%)	181 (14·8%)	0·56	326 (13·6%)	334 (13·8%)	0·83
At 14 days	135 (11·2%)	140 (11·4%)	0·80	249 (10·4%)	259 (10·7%)	0·71
At 28 days	112 (9·3%)	116 (9·5%)	0·88	209 (8·7%)	211 (8·7%)	0·99
RDS confirmed by radiography	241 (20·0%)	266 (21·7%)	0·3	483 (20·2%)	502 (20·8%)	0·60
Treatment with exogenous surfactant	182 (15·1%)	217 (17·7%)	0·08	350 (14·6%)	393 (16·3%)	0·11
O_2 dependence >28 days	111 (9·2%)	114 (9·3%)	0·94	205 (8·6%)	208 (8·6%)	0·95
O_2 at 36 weeks post conception	69 (5·7%)	76 (6·2%)	0·62	136 (5·7%)	142 (5·9%)	0·76
Positive blood culture						
Overall	82 (6·8%)	100 (8·2%)	0·20	165 (6·9%)	168 (7·0%)	0·93
If born within 14 days	63 (5·2%)	85 (6·9%)	0·08	121 (5·1%)	146 (6·0%)	0·13
Necrotising enterocolitis						
Suspected or proven	50 (4·1%)	33 (2·7%)	0·08	92 (3·8%)	58 (2·4%)	0·004
Proven	24 (1·9%)	6 (0·5%)	0·001	44 (1·8%)	17 (0·7%)	0·0005
Abnormal cerebral ultrasonography	46 (3·8%)	61 (5·0%)	0·16	92 (3·8%)	111 (4·6%)	0·19
Deaths	79 (6·6%)	82 (6·7%)	0·89	156 (6·5%)	152 (6·3%)	0·76
Composite primary outcome	163 (13·5%)	186 (15·2%)	0·25	330 (13·8%)	337 (14·0%)	0·87

NICU=neonatal invensive-care unit; SCBU=special-care baby unit; RDS=respiratory distress syndrome.

Table 5: **Neonatal outcomes of babies born to women with pPROM randomly assigned co-amoxiclav**

	Erythromycin and co-amoxiclav (n=1189)	p	Placebo only (n=1225)	p	Any antibiotic* (n=3584)
Delivery within 48 h	372 (31·3%)	<0·0001	498 (40·7%)	<0·0001	1153 (32·1%)
Delivery within 7 days	647 (54·4%)	<0·0001	775 (63·3%)	0·0006	2067 (57·7%)
Gestational age at delivery					
Median (range) gestation (days)	237 (129–296)	. .	236 (142–293)	. .	236 (129–307)
<37 weeks	1018 (85·6%)	0·66	1041 (85·0%)	0·94	3049 (85·1%)
<26 weeks	53 (4·5%)	. .	59 (4·8%)	. .	149 (4·2%)
26–28[6] weeks	97 (8·2%)	. .	113 (9·2%)	. .	296 (8·3%)
29–31[6] weeks	205 (17·2%)	. .	231 (18·9%)	. .	640 (17·9%)
32–36[6] weeks	663 (55·8%)	0·35	638 (52·1%)	0·30	1964 (54·8%)
Mode of delivery					
Spontaneous vaginal	752 (63·2%)	. .	746 (60·9%)	. .	2240 (62·5%)
Forceps/Ventouse	72 (6·1%)	. .	72 (5·9%)	. .	198 (5·5%)
Vaginal breech	58 (4·9%)	. .	50 (4·1%)	. .	172 (4·8%)
Caesarean section	307 (25·8%)	0·28	357 (29·1%)	0·41	974 (27·2%)
Median (range) days in hospital	3 (0–44)	0·12	4 (0–61)	0·21	4 (0–183)
Maternal antibiotic prescription	293 (24·6%)	0·20	330 (26·9%)	0·18	896 (25·0%)
Maternal antibiotic presctiption within 14 days	206 (17·3%)	0·01	262 (21·4%)	0·09	686 (19·1%)

*Erythromycin alone, co-amoxiclav alone, or erythromycin and co-amoxiclav. [6]Number of days.

Table 6: **Maternal outcomes of women with pPROM randomly assigned co-amoxiclav and erythromycin, or any antibiotic**

Proven necrotising enterocolitis was four times higher with co-amoxiclav alone than with placebo, and 2·5 times higher with any co-amoxiclav than with no co-amoxiclav. There were no significant differences in the number of babies with abnormal cerebral ultrasound scans before discharge, or in death. Analysis of the effect of co-amoxiclav prescription on the composite primary outcome showed no benefit (table 5).

The number of women with a multiple pregnancy randomised to each group were as follows: co-amoxiclav only 66, placebo only 76, any co-amoxiclav 143, and no co-amoxiclav 155. No significant differences were detected in any outcome. In an analysis of singleton births, no significant differences in neonatal outcome were detected between the co-amoxiclav only and placebo groups except for admission to intensive or special care (869 [76·3%] *vs* 915 [79·6%], p=0·005), and the total number of babies receiving supplementary oxygen (341 [29·9%] *vs* 389 [33·9%], p=0·05). The only significant differences between the groups assigned any co-amoxiclav and no co-amoxiclav were for admission to intensive or special care (1715 [76·2%] *vs* 1787 [79·1%], p=0·02). There was a significantly higher rate of suspected or proven necrotising enterocolitis (42 [3·7%] *vs* 26 [2·3%], p=0·04) and proven necrotising enterocolitis (18 [1·6%] *vs* 3 [0·3%], p=0·001) with co-amoxiclav only compared with placebo, and also of suspected or proven necrotising entercolitis (74 [3·3%] *vs* 46 [2·0%], p=0·009) and proven necrotising entercolitis (33 [1·5%] *vs* 11 [0·5%], p=0·0007) with any co-amoxiclav compared with no co-amoxiclav.

Erythromycin and co-amoxiclav

In the co-amoxiclav and erythromycin group, and in the group assigned any antibiotic, significantly fewer women delivered within 48 h than did those on placebo. Results were similar for delivery within 7 days (table 6). The number of women receiving antibiotics after delivery and before discharge was significantly lower with the use of both antibiotics than with placebo if delivery occurred within 14 days of randomisation. Use of both antibiotics (60 [5·0%] *vs* 103 [8·4%], p=0·001) and any antibiotic (223 [6·2%] *vs* 103 [8·4%], p=0·008) was associated with significantly less uterine infection than use of placebo.

There were no significant differences in median birthweight, or in the number of babies admitted to intensive or special care between the group assigned both antibiotics and the group assigned any (table 7). For the babies whose mothers were assigned both antibiotics or any antibiotics, significantly fewer received oxygen overall and at 48 h, compared with the babies whose mothers were assigned placebo. Significantly fewer received exogenous surfactant with any antibiotic compared with placebo, but no significant differences were found in the number of babies with markers of chronic lung disease (table 7). Significantly fewer babies in the both antibiotics and any antibiotics groups had positive blood cultures indicative of clinical infection, particularly if the baby was born within 14 days of randomisation, than in the placebo group.

There was a significantly higher proportion of babies with proven necrotising enterocolitis with the use of both antibiotics or any antibiotic than with placebo (table 7). However, there were no significant differences in the proportion of babies with abnormal cerebral ultrasonography before discharge from hospital or in the proportion who died. Analysis of the effect of both or any antibiotic prescription on the composite primary outcome showed no benefit over placebo for women with pPROM (table 7).

The number of women with a multiple pregnancy randomised to each group were as follows: erythromycin and co-amoxiclav 77, placebo only 76, and any antibiotic 222. No significant differences in any outcome were detected. In singleton pregnancies, use of both antibiotics compared with use of placebo was associated with significantly fewer admissions to intensive or special care (846 [76·1%] *vs* 915 [79·6%], p=0·04), less need for any supplementary oxygen (330 [29·7%] *vs* 389 [33·9%], p=0·03), less need for supplementary oxygen at 48 h of age (265 [23·8%] *vs* 319 [27·8%], p=0·03), less treatment with exogenous surfactant (142 [12·8%] *vs* 187 [16·3%], p=0·02), fewer positive blood cultures (57 [5·1%] *vs* 85 [7·4%], p=0·03), but a greater proportion of proven necrotising enterocolitis (15 [1·3%] *vs* three [0·3%], p=0·004). Also for singleton pregnancies, use of any antibiotic compared with use of placebo was associated with significantly less need for any supplementary oxygen (988 [29·4%] *vs* 389 [33·9%], p=0·005), less need for supplementary oxygen at 48 h (803 [23·9%] *vs* 319 [27·8%], p=0·008), less treatment with exogenous surfactant (443 [13·2%] *vs* 187 [16·3%], p=0·009), fewer positive blood cultures (180 [5·4%] *vs* 85 [7·4%], p=0·01), fewer cases of abnormal cerebral ultra-

	Erythromycin and co-amoxiclav (n=1189)	p	Placebo only (n=1225)	p	Any antibiotic* (n=3584)
Birthweight (g)					
Mean (SD)	2123 (770)	0·11	2072 (769)	0·22	2103 (764)
Median (range)	2100 (180–4710)	. .	2055 (240–4366)	. .	2080 (180–4710)
<2500	841 (70·7%)	0·55	880 (71·8%)	0·90	2581 (72·0%)
<1500	250 (21·0%)	0·20	284 (23·2%)	0·27	776 (21·7%)
Admission to NICU/SCBU	818 (68·8%)	0·10	880 (71·8%)	0·18	2502 (69·8%)
Total babies ventilated	244 (20·5%)	0·13	283 (23·1%)	0·11	749 (20·9%)
Total babies in >21% O_2	372 (31·3%)	0·03	436 (35·6%)	0·007	1125 (31·4%)
At 48 h	305 (25·7%)	0·05	358 (29·2%)	0·02	923 (25·8%)
At 7 days	158 (13·3%)	0·29	181 (14·8%)	0·22	479 (13·4%)
At 14 days	114 (9·6%)	0·14	140 (11·4%)	0·25	368 (10·3%)
At 28 days	97 (8·2%)	0·25	116 (9·5%)	0·29	304 (8·5%)
RDS confirmed by radiography	242 (20·4%)	0·41	266 (21·7%)	0·22	719 (20·1%)
Treatment with exogenous surfactant	168 (14·1%)	0·02	217 (17·7%)	0·01	526 (14·7%)
O_2 dependence >28 days	94 (7·9%)	0·22	114 (9·3%)	0·3	299 (8·3%)
O_2 at 36 weeks post conception	67 (5·6%)	0·56	76 (6·2%)	0·45	202 (5·6%)
Positive blood culture					
Overall	83 (7·0%)	0·27	100 (8·2%)	0·05	233 (6·5%)
If born within 14 days	58 (4·9%)	0·03	85 (6·9%)	0·01	182 (5·1%)
Necrotising enterocolitis					
Suspected or proven	42 (3·5%)	0·23	33 (2·7%)	0·32	117 (3·3%)
Proven	20 (1·7%)	0·005	6 (0·5%)	0·005	55 (1·5%)
Abnormal cerebral ultrasonography	46 (3·9%)	0·18	61 (5·0%)	0·13	142 (4·0%)
Deaths	77 (6·5%)	0·83	82 (6·7%)	0·63	226 (6·3%)
Composite primary outcome	167 (14·0%)	0·43	186 (15·2%)	0·12	481 (13·4%)

NICU=neonatal intensive-care unit; SCBU=special-care baby unit; RDS=respiratory distress syndrome. *Erythromycin alone, co-amoxiclav alone, or erythromycin and co-amoxiclav.

Table 7: **Neonatal outcomes of women with pPROM randomly assigned co-amoxiclav and erythromycin, or any antibiotic**

sonography (110 [3·3%] *vs* 53 [4·6%], p=0·04), and fewer instances of the composite primary outcome (406 [12·1%] *vs* 166 [14·4%], p=0·04). However, there was a significantly greater number of cases of necrotising enterocolitis (41 [1·2%] *vs* three [0·3%], p=0·004).

A subgroup analysis was done on women who were randomised at less than 32 weeks' gestation. The same pattern of results was found as in the main analysis. Analyses were also done on women enrolled in UK maternity units and on those enrolled at international maternity units for prolongation of pregnancy and the composite primary outcome; no significant differences were detected between the two groups.

Discussion

The results of this trial indicate a range of health benefits, particularly for singleton pregnancies, with the prescription of erythromycin, including reduction in delivery at 7 days after randomisation, reduction in neonatal treatment with surfactant, reduction in the rate of positive neonatal blood cultures, reduction in chronic lung disease (neonatal ventilation or oxygen at >28 days of age), reduction in the rate of major cerebral abnormality by ultrasonography, and reduction in the composite primary outcome of death, chronic lung disease, and major cerebral abnormality. Although erythromycin was less effective than co-amoxiclav at prolonging pregnancy and reducing maternal infection, there was better evidence of its beneficial effect on neonatal disease, and there was no evidence of harm.

In contrast, co-amoxiclav was associated with a significant increase in the occurrence of neonatal necrotising enterocolitis. This finding was also seen, although to a lesser extent, in the concurrent trial of co-amoxiclav in spontaneous preterm labour.[9] On scrutiny of the Cochrane review,[6] only one previous trial (which was published only as an abstract) assessed the use of co-amoxiclav. In this trial of 62 participants,[12] there were five cases of neonatal necrotising enterocolitis in the co-amoxiclav group, and no cases in the placebo group. This effect is plausible, since co-amoxiclav is known to select for *Clostridium difficile* (a cause of pseudomembranous colitis) in adults. One suggested mechanisms of pathogenesis of neonatal necrotising enterocolitis is abnormal microbial colonisation of the intestinal tract by one or a few species unhindered by competitors.[13] Co-amoxiclav, because of its range of activity and effectiveness, can facilitate such colonisation. Furthermore, the immature gut is able to absorb any exotoxins produced intact, resulting in mucosal damage and the initiation of necrotising enterocolitis. We therefore do not recommend routine prescription of co-amoxiclav for any preterm delivery, whether it be a preterm prelabour rupture of the membranes, spontaneous preterm labour, or caesarean section for preterm delivery. Additionally, its use in the neonatal period should be examined.

The results also show that indicators of short-term neonatal respiratory distress syndrome and chronic lung disease are reduced by erythromycin. These beneficial effects might merely be a result of prolonging pregnancy, but they might have a more direct basis. There is evidence that lung inflammation or infection can be essential in the pathogenesis of neonatal respiratory distress syndrome and chronic lung disease. Studies of the constituents of bronchoalveolar lavage fluid from infants who develop neonatal respiratory distress syndrome and recover, compared with those who progress to chronic lung disease, have shown that infants who develop chronic lung disease have higher concentrations of neutrophils,[14] proinflammatory cytokines (including interleukin 1, interleukin 6, interleukin 8),[15,16] and proxy markers of neutrophil recruitment such as soluble L-selectin and soluble intercellular adhesion molecule 1 in the broncho-alveolar lavage fluid at 7–10 days of age, than those who recover from respiratory distress syndrome.[15,17] Moreover,

there is evidence that intrauterine lung inflammation is implicated in the genesis of chronic lung disease, since high concentrations of the potent profibrotic agent transforming growth factor β have been described in the first bronchoalveolar lavage fluid after birth of infants who go on to develop chronic lung disease.[18,19] Further evidence that intrauterine infection or inflammation of the lung is related to the pathogenesis of neonatal respiratory distress syndrome and chronic lung disease comes from these disorders' associations with the presence of *Ureaplasma urealyticum*.[20] The health benefits of erythromycin in pPROM are therefore not likely to be due merely to prolongation of pregnancy, but to a reduction of the effects of fetal and neonatal lung infection or inflammation. We are currently planning a long-term follow-up study to find out whether childhood respiratory disease is reduced by erythromycin for pPROM.

The decrease in the occurrence of major neonatal cerebral abnormality could also be due to prolongation of pregnancy alone, or to the effect of erythromycin's reduction of intrauterine infection or inflammation on the fetal and neonatal brain. Again, there is evidence to implicate intrauterine infection or inflammation in fetal and neonatal cerebral damage. Histological chorioamnionitis,[21–23] and funisitis with raised concentrations of interleukin 6 and interleukin 8 in amniotic fluid[24] have been associated with cerebral palsy. Additionally, raised concentrations of umbilical-cord interleukin 6 have been found in neonates with ultrasonographic evidence of periventricular leucomalacia.[25] The preliminary results of a study of more than 40 infants with very low birthweights showed a strong association between indicators of chorioamnionitis and damage to cerebral white matter.[26] Additionally, concentrations of proinflammatory cytokines and CD40-RO-positive T cells (a marker of exposure to antigen) were higher in cord blood from infants with damage to white matter than in infants without such damage.

The importance of potential effects of pPROM on brain development in children is illustrated by the results of two clinical studies. In the first, Murphy and colleagues[22] did a case-control study of 59 children with cerebral palsy who were singleton and less than 32 weeks of gestation at birth. They found that the three most important antenatal risk factors were prolonged (>24 h) rupture of the membranes (odds ratio 2·3 [95% CI 1·2–4·2]), chorioamnionitis (4·2 [1·4–12·0]), and maternal infection (2·3 [1·2–4·5]). Results of the second report[27] showed a five-fold increase in the likelihood of severe neurological handicap in infants born after pPROM at between 24 and 34 weeks' gestation, compared with infants who had been born after spontaneous preterm labour, and that the risk of handicap was related to the duration of membrane rupture.

Since erythromycin for pPROM seems to have some beneficial effect on the rate of ultrasound-identified cerebral abnormality, which is known to greatly underestimate cerebral damage,[28] we plan to determine what effect erythromycin given for pPROM has on childhood neuromotor and cognitive function, and whether disability is decreased.

Our results show that a cheap and widely available antibiotic, erythromycin, when given to women with pPROM, has effects on the occurrence of major neonatal disease, and might therefore have a substantial health benefit on the long-term respiratory and neurological function of many children.

Contributors

Sara Kenyon (Leicester, UK), David Taylor (Leicester), Richard Peto (Oxford, UK), and William Tarnow-Mordi (Sydney, Australia) designed the study protocol. David Taylor and Sara Kenyon supervised the study. Sara Kenyon and the trial team took responsibility for the day-to-day contact with the centres, the organisation of the drug supplies, and the management of the data. The statistical analysis was done by Ann Blackburn, supported by Richard Peto.

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