Antibiotics did not prevent adverse outcomes after preterm, prelabor rupture of fetal membranes

Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. **Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial.** Lancet. 2001 Mar 31;357:979-88.

QUESTION

In pregnant women with preterm, prelabor rupture of fetal membranes (pPROM), are antibiotics better than placebo for preventing neonatal death, chronic lung disease, or major cerebral abnormality before discharge?

DESIGN

Randomized {allocation concealed*}†, blinded (patients, clinicians {outcome assessors, and statisticians}†),* placebo-controlled trial with a median follow-up of 4 days.

SETTING

161 centers in 15 countries.

PATIENTS

4826 pregnant women who had fetuses that were < 37 weeks of gestation, had pPROM, and had an uncertain need for antibiotics. Women who would have immediate or unstoppable delivery or who had fetuses not premature enough to warrant concern, had medical or drug contraindications, were prescribed antibiotics, or who were to be prescribed antibiotics for infection were excluded. 4809 women (mean age 28 y) were studied after exclusion of 15 women for protocol violations and 2 women for loss to follow-up.

INTERVENTION

1197 women were allocated to erythromycin, 250 mg; 1212 were allocated to co-amoxiclav, 325 mg (composed of amoxicillin, 250 mg, plus clavulanic acid, 125 mg); 1192 were allocated to combined co-amoxiclav, 325 mg, and erythromycin, 250 mg; and 1225 were allocated to placebo. All treatments were taken orally 4 times daily for 10 days or until delivery.

MAIN OUTCOME MEASURE

Composite measure of neonatal death, chronic lung disease (received daily supplementary oxygen at 36 weeks after conception), or major cerebral abnormality on ultrasonography before discharge.

MAIN RESULTS

Analysis was by intention to treat. Erythromycin, co-amoxiclav, and combined treatments were not better than placebo for preventing occurrence of the composite measure before discharge (Table).

CONCLUSION

In pregnant women with preterm, prelabor rupture of fetal membranes, erythromycin, co-amoxiclav, or combined treatments were not better than placebo for preventing the composite outcome measure of neonatal death, chronic lung disease, or major cerebral abnormality before discharge.

Sources of funding: U.K. Medical Research Council. Co-amoxiclav (Augmentin) and co-amoxiclav placebo were supplied by SmithKline Beecham; erythromycin (Erymax) and erythromycin placebo were supplied by Parke-Davis.

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*See Glossary.

†Information provided by author.

Erythromycin (Ery), co-amoxiclav (Co-amx), and combined treatments vs placebo (Pl) for the composite outcome measure of death, chronic lung disease, or major cerebral abnormality in neonates of women who had pPROM‡

Comparison	Event rates	RRR (95% CI)	NNT
Ery vs Pl	12.7% vs 15.2%	16.4% (–2.0 to 31.5)	Not significant
Co-amx vs Pl	13.5% vs 15.2%	10.9% (–8.2 to 26.7)	Not significant
Combined vs Pl	14.0% vs 15.2%	7.5% (–12.2 to 23.7)	Not significant

‡pPROM = preterm, prelabor rupture of fetal membranes. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

At the beginning of the 21st century, preterm delivery remains the major perinatal challenge. Even mildly and moderately premature infants are at high relative risk for death (1). Widespread uncertainty exists about the benefits and risks of antibiotic use for women in spontaneous labor with intact membranes and for those with pPROM. The findings of these studies by Kenyon and colleagues (ORACLE I and II) are therefore highly relevant to practitioners and those planning future research.

The authors have enrolled unprecedented numbers of women in preterm labor in their placebo-controlled trial (> 4 times the number of women included in all previous randomized controlled trials in this area). However, details are not given of eligible patients who were not offered or who declined entry to the trial, and information is not available about the proportions of women in participating hospitals who were considered "ineligible" because antibiotics had already been prescribed or were considered necessary. If large numbers of women were already receiving antibiotics, this would limit the generalizability of the results, with those entered in ORACLE possibly representing a group who were "less at risk." This possibility may explain the finding that two-thirds of the mothers in ORACLE II delivered at term as well as the finding of low overall mortality (about 2.5%). In previous studies on antibiotics in preterm labor cited in the Cochrane review, the overall mortality was 15% (2). Use of a predictive test, such as fetal fibronectin, may have allowed identification of a higher-risk group. However, in ORACLE I, in which the entry criterion of "ruptured membranes" was more clearly defined, the mortality rate was about 6.3%, which compares with the meta-analyzed rate of 7.6% (3).

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Antibiotics did not prevent adverse outcomes in women in preterm labor with intact fetal membranes

Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. **Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial.** Lancet. 2001 Mar 31;357:989-94.

QUESTION

For pregnant women in preterm labor with intact fetal membranes, are antibiotics better than placebo for preventing neonatal death, chronic lung disease, or major cerebral abnormality before discharge?

DESIGN

Randomized {allocation concealed*}†, blinded (patients, clinicians {outcome assessors, and statisticians}†),* placebo-controlled trial with a median follow-up of 4 days.

SETTING

161 centers in 15 countries.

PATIENTS

6295 pregnant women who had fetuses that were < 37 weeks of gestation, who were in suspected or definite preterm labor with intact fetal membranes, and who had an uncertain need for antibiotics. Women who would have immediate or unstoppable delivery or who had fetuses not premature enough to warrant concern, had medical or drug contraindications, were prescribed antibiotics, or who were to be prescribed antibiotics for infection were excluded. 6241 women (mean age 26 y) were studied after exclusion of 14 women for protocol violations and 40 women for loss to follow-up.

INTERVENTION

1611 women were allocated to erythromycin, 250 mg; 1550 were allocated to co-amoxiclav, 325 mg (composed of amoxicillin, 250 mg, plus clavulanic acid, 125 mg); 1565 were allocated to combined co-amoxiclav, 325 mg, and erythromycin, 250 mg; and 1569 were allocated to placebo. All treatments were taken orally 4 times daily for 10 days or until delivery.

MAIN OUTCOME MEASURE

Composite measure of neonatal death, chronic lung disease (received daily supplementary oxygen at 36 weeks after conception), or major cerebral abnormality on ultrasonography before discharge.

MAIN RESULTS

Analysis was by intention to treat. Erythromycin, co-amoxiclav, and combined treatments were not better than placebo for preventing occurrence of the composite measure before discharge (Table).

CONCLUSION

For pregnant women in preterm labor with intact fetal membranes, erythromycin, co-amoxiclav, or combined treatments were not better than placebo for preventing the composite outcome measure of neonatal death, chronic lung disease, or major cerebral abnormality before discharge.

Sources of funding: U.K. Medical Research Council. Co-amoxiclav (Augmentin) and co-amoxiclav placebo were supplied by SmithKline Beecham; erythromycin (Erymax) and erythromycin placebo were supplied by Parke-Davis.

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*See Glossary.

†Information provided by author.

Co-amoxiclav (Co-amx), erythromycin (Ery), and combined treatments vs placebo (Pl) for the composite outcome measure of death, chronic lung disease, or major cerebral abnormality in neonates of women who were in preterm labor‡

Comparison	Event rates	RRR (95% CI)	NNT
Co-amx vs Pl	4.95% vs 5.01%	1.2% (–34.3 to 27.3)	Not significant
		RRI (CI)	NNH
Ery vs Pl	5.63% vs 5.01%	12.2% (–16.4 to 50.6)	Not significant
Combined vs Pl	5.87% vs 5.01%	17.0% (–12.7 to 56.9)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY *(continued from page 69)*

Groups did not differ for the main outcome in either ORACLE I or II. Secondary analyses in women with pPROM suggested a number of benefits. Although these findings may indeed be the result of chance (4), they mirror trends seen in the meta-analysis (3). Given the growing body of evidence that intrauterine infection is linked to long-term adverse outcome and the absence of findings to show harm associated with erythromycin treatment, it is highly likely that prophylactic treatment in this situation will become standard. Similarly, clinicians would be wise to avoid the use of Augmentin (co-amoxiclav) in these situations.

The authors, in discussing the negative findings of ORACLE II, suggest future research in relation to screening for bacterial vaginosis and subsequent antibiotic treatment. It is worth noting that another trial with negative results has recently been published (5).

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