Antibiotics for pPROM: Few Benefits, Significant Risks

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

Study Overview

Objective. To determine whether the use of broad-spectrum oral antibiotics provides any benefit to newborns or their mothers in the setting of preterm, prelabor rupture of fetal membranes (pPROM).

Design. Double-blind, placebo-controlled, randomized clinical trial. Analysis was by intention to treat.

Setting and participants. 4826 women with pPROM from 161 participating centers were enrolled in the study. 4447 women (92%) were from the United Kingdom and 379 were from collaborating centers in other countries. Women were eligible if the gestational age of their fetuses was less than 37 weeks and if the need to prescribe antibiotics was uncertain. (Reasons for prescribing antibiotics were not included in the article.) Exclusion criteria were antibiotics already prescribed, immediate delivery desirable or unstoppable, fetus not premature enough to cause concern, and presence of contraindications to erythromycin (eg, allergy, jaundice, use of medications with known interactions) or amoxicillin (eg, allergy).

Intervention. Women were assigned to 250 mg erthromycin, 325 mg co-amoxiclav (250 mg amoxicillin plus 125 mg clavulanic acid), both, or placebo in a 2×2 factorial design. Study agents were to be taken 4 times daily for 10 days or until delivery.

Main outcome measures. The primary outcome was a composite measure of certain adverse events affecting the newborn prior to hospital discharge, including death, chronic lung disease (defined as a need for supplemental oxygen at 36 weeks past gestation), or major cerebral abnormality on ultrasonography. Secondary outcomes included many maternal and newborn variables, such as time of delivery, birth weight, and markers of infectious and other complications.

Main results. Of the 4826 women randomized, 2 were lost to follow-up and 15 were excluded due to protocol violations. The remaining women, on average, were about 28 years old. Median gestation at baseline was 32 weeks, and most women (76.5%) were receiving steroids for maturation of fetal lungs. No significant difference in the primary outcome was observed between mothers receiving either or both antibiotics and mothers receiving placebo. Four of 28 secondary outcome variables (delivery within 48 hours or within 7 days, treatment with exogenous surfactant, and positive neonatal blood culture) reached statistical significance when comparing erythromycin alone or with co-amoxiclav to placebo. In a post hoc subgroup analysis of singleton births, several other variables reached a P of 0.05 or less. Analysis of groups receiving co-amoxiclav found similar outcomes in the principle analysis but no additional statistically significant findings in subgroup analyses. In addition, co-amoxiclav was associated with a fourfold higher incidence of necrotizing enterocolitis (P not reported).

Conclusion. Erythromycin for women with pPROM provides some health benefits to the neonate. Amoxicillin with clavulanic acid may be associated with clinically significant risks.

Commentary

This was an excellent study designed to detect small but clinically significant advantages (or disadvantages) associated with the antibiotics examined. The authors concluded that erythromycin has some benefit and should be used in most women with pPROM who have no contraindications. However, an editorialist [1] pointed out that the associations that reached a level of statistical significance ($P \leq 5$)—especially those in the post hoc subgroup analyses—could have been due to chance. When examining so many variables, more stringent criteria should be used to determine significance. If the authors had done this, the only finding that clearly reached significance was delay in premature delivery with antibiotic use. Because of such discrepancies, the editorialist disagrees with Kenyon et al's conclusion

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Applications for Clinical Practice

An accompanying article [2], also from the ORACLE Collaborative Group, reported that the same antibiotics (erythromycin and co-amoxiclav) did not provide any benefit for women with spontaneous preterm labor. Together, these studies provide fairly definitive evidence that antibiotics should be used only when there is a clear infectious indication in women with pPROM or spontaneous preterm labor.

References

1. Hannah M. Antibiotics for preterm prelabour rupture of membranes and preterm labour? Lancet 2001;357:973–4.
2. Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group. Lancet 2001;357: 989–94.