Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials

Pitsouni E, Iavazzo C, Athanasiou S, Falagas M E

CRD summary
The authors conclude that azithromycin is as effective as erythromycin or amoxicillin for treating Chlamydia trachomatis in pregnancy and has fewer adverse effects. Although the data appear to support these conclusions, they should be interpreted with some caution given the limitations in the search and failure to adequately address inconsistencies between the primary studies.

Authors’ objectives
To assess the effectiveness and safety of azithromycin for the treatment of pregnant women with Chlamydia trachomatis (C. trachomatis) infection, compared with erythromycin or amoxicillin.

Searching
PubMed and Scopus were searched from 1991 to 2006 for articles published in English; the search terms were reported. Conference abstracts were only included if they appeared in publications retrieved from the search.

Study selection
Randomised controlled trials (RCTs) comparing azithromycin with erythromycin or amoxicillin for the treatment of C. trachomatis infection were eligible for inclusion. The primary comparison was between azithromycin and erythromycin, but azithromycin was also compared with treatment using either erythromycin or amoxicillin (erythromycin/amoxicillin). In all the included studies, a single oral (p.o.) dose of azithromycin (1 g) was used. The control interventions comprised erythromycin (500 mg p.o. three or four times daily for 7 days) or amoxicillin (500 mg p.o. three times daily for 7 days). The participants in eligible studies were pregnant women with symptomless C. trachomatis infection diagnosed by positive cultures from routine screening at the first prenatal visit and early in the third trimester. The demographics of women in the included studies were similar. All studies advised partners who tested positive for C. trachomatis to receive treatment and to take precautions with regard to sexual intercourse. The review reported on treatment success, perinatal or neonatal outcomes, and gastrointestinal (GI) or other adverse events. Treatment success was defined in the review as negative C. trachomatis cultures 2 to 6 weeks after treatment at a test-of-cure visit. The perinatal outcomes of interest were pre-term delivery and premature rupture of membranes (PROM). The neonatal outcomes of interest were stillbirth, neonatal death, polydactyly, ventricular septal defect and serious anomalies of the newborn. The GI adverse events of interest were vomiting, nausea, anorexia, abdominal pain and diarrhoea; other adverse events were rash, pruritis, cramping and dizziness. Other outcomes reported in the review included withdrawal rates, compliance with therapy and cost. In most (but not all) studies, withdrawal rates appeared to refer to withdrawal due to severe adverse events. Timing of the outcomes assessment differed in the included studies; cervical cultures assessing cure were obtained at differing intervals, ranging from 2 to 6 weeks after completion of therapy.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
A modified Jadad score was used to assess the quality of the included studies. One point was allocated for each of the following factors: randomisation, generation of random numbers, details of double-blinding procedure, information on withdrawals, and concealment of allocation. High-quality RCTs scored over 2 points, while low-quality RCTs scored 2 or fewer points.

Two reviewers independently assessed the validity of the included studies.

Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all outcomes. Two reviewers independently extracted the data from the included studies.

**Methods of synthesis**
The authors reported that the data analysis was based on a previous study (Siempos et al. 2007) in which ORs were pooled using a DerSimonian and Laird random-effects model to calculate a pooled OR with 95% CI. Statistical heterogeneity was assessed using the $\chi^2$ test ($p=0.10$ denoting statistical significance). Publication bias was assessed using funnel plots and Egger's test ($p=0.05$ denoting statistical significance). For some outcomes in the current review, data were pooled separately for intention-to-treat participants (defined as those who received at least one dose of study medication) and for clinically evaluated participants (those who completed the study protocol).

**Results of the review**

Eight RCTs ($n=587$) were included, of which seven were published and one was a conference abstract.

Five RCTs scored 4 out of a possible 5 points for quality on the modified Jadad scale and three scored 2 points. All RCTs were described as randomised and provided details of withdrawals. Five reported the generation of random numbers and concealment of allocation. Two RCTs were single-blinded; none were double-blinded. No publication bias was detected in any analysis.

There was no statistically significant difference in treatment success between the groups when azithromycin was compared with erythromycin (OR 2.66, 95% CI: 0.69, 10.29; 4 RCTs, $n=293$) or erythromycin/amoxicillin (OR 1.45, 95% CI: 0.82, 2.57; 6 RCTs, $n=344$). Cure rates ranged from 63 to 100% for azithromycin, from 72 to 94% for erythromycin, and from 58 to 80% for amoxicillin.

There were fewer GI adverse events in the azithromycin group than in the erythromycin group (OR 0.11, 95% CI: 0.07, 0.18; 6 RCTs, $n=374$) or the erythromycin/amoxicillin group (OR 0.16, 95% CI: 0.06, 0.4; 7 RCTs, $n=412$). There was no statistically significant difference between the groups in the incidence of other adverse events when azithromycin was compared with erythromycin (5 RCTs, $n=334$) or with erythromycin/amoxicillin (7 RCTs, $n=482$). There were significantly fewer total adverse events in the azithromycin group than either the erythromycin group (OR 0.11, 95% CI: 0.07, 0.18; 5 RCTs, $n=289$) or the erythromycin/amoxicillin group (OR 0.13, 95% CI: 0.08, 0.21; 6 RCTs, $n=325$).

There were significantly fewer withdrawals in the azithromycin group than in the erythromycin group (OR 0.12, 95% CI: 0.04, 0.37; 4 RCTs, $n=203$). In three of these RCTs, withdrawals comprised women who were unable to tolerate the intervention because of severe adverse effects, while in the fourth the dose of erythromycin was reduced to 250 mg to allow women to complete the protocol. There was no statistically significant difference in withdrawals between the groups when azithromycin was compared with erythromycin/amoxicillin (6 RCTs, $n=352$).

Women in the azithromycin group were more compliant with therapy than those in the erythromycin group (OR 23.7, 95% CI: 9.34, 60.14; 6 RCTs, $n=374$) or in the erythromycin/amoxicillin group (OR 21.96, 95% CI: 9.05, 53.3; 7 RCTs, $n=413$).

There was no significant difference in neonatal outcomes between the groups when azithromycin was compared with erythromycin (2 RCTs, $n=246$).

**Cost information**

Three RCTs reported higher costs for the total dose of therapy for azithromycin compared with erythromycin ($15 versus $5) or amoxicillin ($26 versus $7, $68 versus $8).

**Authors' conclusions**

Azithromycin is as effective as erythromycin or amoxicillin for the treatment of *C. trachomatis* infection in pregnant women and is associated with fewer adverse events. In view of the higher cost of azithromycin, cost-effectiveness studies may be warranted.

**CRD commentary**

The review objectives and inclusion criteria were clear but the literature search was limited to two databases; this may
mean that some studies were missed. Moreover, the restriction to studies in English might have created language bias. Adequate details were provided about the included studies and relevant aspects of study quality were considered, though it is unclear whether all relevant quality criteria were assessed systematically (e.g. the use of intention-to-treat analysis, prognostic balance at baseline). Steps were taken to minimise error and bias in the review process by having two reviewers make decisions independently, though it is not stated how any discrepancies were resolved. The statistical methods used to pool the studies and the methods proposed for the assessment of heterogeneity and publication bias appear appropriate. However, the forest plots for treatment success showed differing directions of effect among the primary studies and it is unclear whether reasons for this apparent heterogeneity were considered or whether it was evaluated statistically. Although the data appear to support the authors’ conclusions, they should be interpreted with some caution given the limitations in the search and failure to adequately address apparent inconsistencies between the primary studies.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that a formal cost-effectiveness analysis of the use of azithromycin for treating C. trachomatis in pregnant women may be worthwhile. They also suggested that the optimum course of erythromycin therapy for the treatment of C. trachomatis should be investigated, since cure rates with erythromycin were comparable with those of azithromycin despite lower compliance rates.

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