OBSTETRICS

Antibiotic prophylaxis for term or near-term premature rupture of membranes: metaanalysis of randomized trials

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OBJECTIVE: The objective of the study was to evaluate the efficacy of antibiotic prophylaxis in women with term or near-term premature rupture of membranes.

STUDY DESIGN: Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, ScienceDirect.com, MEDSCAPE, and the Cochrane Central Register of Controlled Trials with the use of a combination of key words and text words related to antibiotics, premature rupture of membranes, term, and trials from inception of each database to September 2014. We included all randomized trials of singleton gestations with premature rupture of membranes at 36 weeks or more, who were randomized to antibiotic prophylaxis or control (either placebo or no treatment). The primary outcomes included maternal chorioamnionitis and neonatal sepsis. A subgroup analysis on studies with latency more than 12 hours was planned. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42014013928). The metaanalysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses statement.

RESULTS: Women who received antibiotics had the same rate of chorioamnionitis (2.7% vs 3.7%; relative risk [RR], 0.73, 95% confidence interval [CI], 0.48–1.12), endometritis (0.4% vs 0.9%; RR, 0.44, 95% CI, 0.18–1.10), maternal infection (3.1% vs 4.6%; RR, 0.48, 95% CI, 0.19–1.21), and neonatal sepsis (1.0% vs 1.4%; RR, 0.69, 95% CI, 0.34–1.39). In the planned subgroup analysis, women with latency longer than 12 hours, who received antibiotics, had a lower rate of chorioamnionitis (2.9% vs 6.1%; RR, 0.49, 95% CI, 0.27–0.91) and endometritis (0% vs 2.2%; RR, 0.12, 95% CI, 0.02–0.62) compared with the control group.

CONCLUSION: Antibiotic prophylaxis for term or near-term premature rupture of membranes is not associated with any benefits in either maternal or neonatal outcomes. In women with latency longer than 12 hours, prophylactic antibiotics are associated with significantly lower rates of chorioamnionitis by 51% and endometritis by 88%.

Key words: antibiotic prophylaxis, chorioamnionitis, metaanalysis, neonatal sepsis, premature rupture of membranes

Cite this article as: Saccone G, Berghella V. Antibiotic prophylaxis for term or near-term premature rupture of membranes: metaanalysis of randomized trials. Am J Obstet Gynecol 2015;212:627.e1-9.

Premature rupture of the membranes (PROM), defined as the rupture of the membranes before the onset of labor, occurs in approximately 8% of pregnancies at term (ie, ≥37 weeks).[1] PROM has been associated with increased risks of infection for both the mother (eg, chorioamnionitis and endometritis) and her baby (eg, neonatal sepsis).[2]

Despite these infectious risks, the current management of term PROM does not include prophylactic antibiotics, whereas that of preterm PROM (ie, <34 weeks) does include antibiotics prophylaxis.[2] The recommendation of antibiotic prophylaxis in preterm PROM stems from level 1 evidence of their significant association with reductions in chorioamnionitis and neonatal infection and with prolongation of pregnancy.[3]

The only recommended management for term PROM based on level 1 evidence is currently induction of labor.[2] There is instead little information about the efficacy of antibiotics in term or near-term PROM, despite its infectious risks, and the evidence regarding their efficacy in preterm PROM.

The aim of this metaanalysis was to evaluate the efficacy of antibiotic prophylaxis in women with term or near-term PROM.

Materials and Methods

The research protocol was designed a priori, defining methods for searching the literature, including and examining articles, and extracting and analyzing data. Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, ScienceDirect.com, MEDSCAPE, and the Cochrane Central Register of Controlled Trials with the use of a combination of key words and text words related to antibiotics, premature rupture of membranes, term, and trials from the

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Received Oct. 7, 2014; revised Nov. 22, 2014; accepted Dec. 21, 2014.

The authors report no conflict of interest.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2014.12.034

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inception of each database to September 2014. No restrictions for language or geographic location were applied.

We included all randomized controlled trials (RCTs) of singleton gestations with PROM at 36 weeks or more, who were randomized to antibiotic prophylaxis or control (either placebo or no treatment). All published randomized studies on antibiotic prophylaxis for patients with term or near-term PROM were carefully reviewed. Exclusion criteria included quasirandomized trials, trials in women with preterm PROM, trials that were restricted to only group B streptococcus–positive women, trials using antibiotics no longer recommended in pregnancy, and trials in which antibiotics were used also in a control group.

Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42014013928). The metaanalysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[4]

Data abstraction was completed by 2 independent investigators (G.S. and V.B.). Each investigator independently abstracted data from each study and analyzed the data separately. Differences were reviewed and further resolved by common review of the entire data. Authors were contacted for missing data.

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (The Cochrane Collaboration's tool for assessing risk of bias). Seven domains related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with the following biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as low risk, high risk, or unclear risk of bias.[5]

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The outcomes were chosen to reflect maternal morbidity, obstetric intervention, and perinatal morbidity and mortality. Primary outcomes were maternal chorioamnionitis and neonatal sepsis (with or without positive blood cultures).

Maternal secondary outcomes included latency, cesarean delivery (CD), endometritis, postpartum septicemia, placental abruption, induction of labor, spontaneous labor, cord prolapse, days of hospitalization, breast-feeding, and maternal adverse drug reaction. Secondary neonatal outcomes included admission to the neonatal intensive care unit (NICU), respiratory complications, abnormality on cerebral ultrasound (either cystic periventricular leukomalacia or intraventricular hemorrhage), cerebral palsy, the rate of neonates who required antibiotics, neonatal infection/sepsis, Apgar score less than 7 at 5 minutes, and perinatal death. Because the rate of maternal and perinatal infection increases with longer times from admission to delivery, a subgroup analysis on the studies with latency more than 12 hours was planned.[6]

The data analysis was completed independently by the authors (G.A. and V.B.) using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved with a review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Cochrane Q statistic and Higgins I^2 statistics.

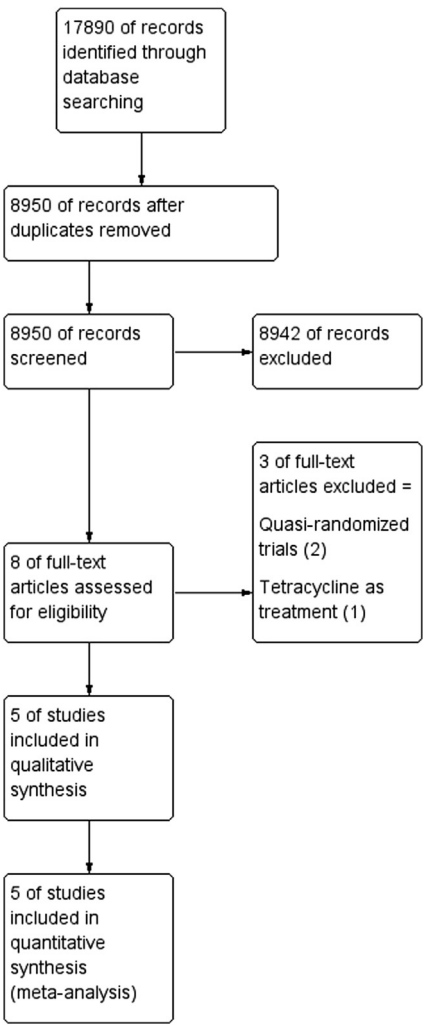
In case of statistical significant heterogeneity (a value of the Cochrane Q statistic of $P < .1$), the random effects model of DerSimonian and Laird[5] was used to obtain the pooled risk ratio (RR) estimate; otherwise a fixed-effect models was planned. The summary measures were reported as RR with a 95% confidence interval (CI). A value of $P < .05$ was considered statistically significant.

This study had no funding source.

Results

We identified 8 trials on antibiotic prophylaxis in term or near-term PROM.[7-14] Three were excluded[7-9]: 2 were excluded because they were quasirandomized trials,[8,9] and 1 was excluded because the antibiotic used (tetracycline) is no longer recommended for use in pregnancy.[7] Five trials, which met inclusion criteria for this metaanalysis, were included.[10-14] Figure 1 shows the flow diagram (PRISMA template) of information through the different phases of the review. The authors of one of these included trials provided the requested additional information.[10]

FIGURE 1
Flow diagram of studies identified in the systematic review (PRISMA template)



PRISMA, Preferred Reporting Item for Systematic Reviews and Meta-analyses.

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