OBSTETRICS

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

Gabriele Saccone, MD; Vincenzo Berghella, MD

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

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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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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.

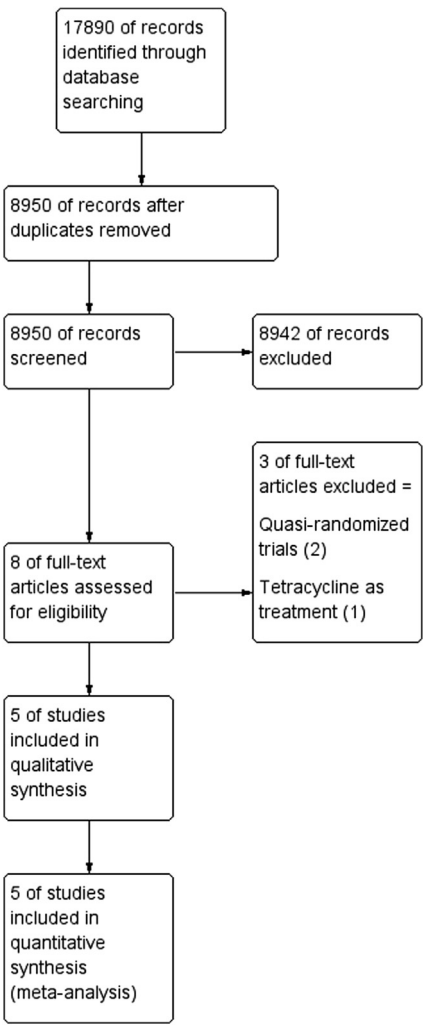
In case of statistical significant heterogeneity (a value of the Cochrane Q statistic of $P < .1$), the random effects model of DerSimonian and Laird[5] was used to obtain the pooled risk ratio (RR) estimate; otherwise a fixed-effect models was planned. The summary measures were reported as RR with a 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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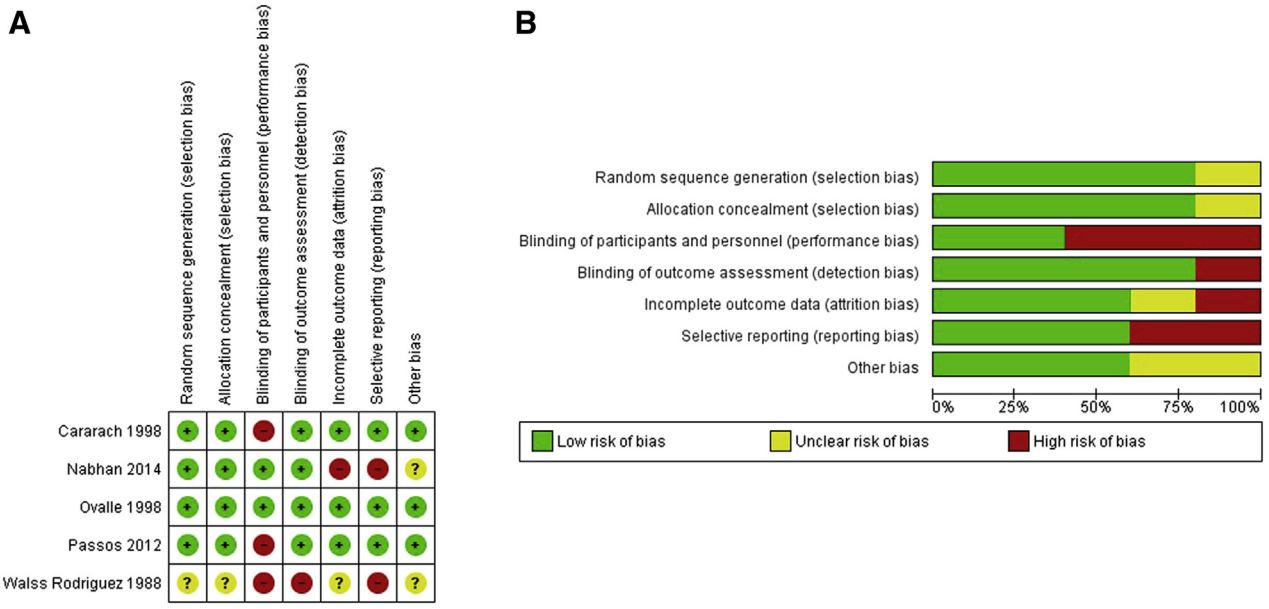
FIGURE 2
Assessment of risk of bias



A, Summary of the risk of bias for each trial. **B**, Risk of bias graph about each risk of bias item presented as percentages across all included studies. The *minus sign* indicates high risk of bias; *plus sign* indicates low risk of bias; question mark indicates unclear risk of bias.

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TABLE 1
Descriptive data of included trials

Variable	Walss Rodriguez and Navarro Castanon, 1988[14]	Cararach et al, 1998[11]	Ovalle et al, 1998[10]	Passos et al, 2012[12]	Nabhan et al, 2014[13]	Total
Study location	Mexico	Spain	Chile	Portugal	Egypt	—
Patients at randomization, n	60 (30/30)	733 (371/362)	105 (55/50)	161 (78/83)	1640 (820/820)	2699 (1354/1345)
GA at randomization (wks^{days})	$\geq 37^{0}$	$\geq 36^{0}$	37^{0}–42^{6}	$\geq 37^{0}$	$\geq 36^{0}$	—
GBS status	N/A	N/A	N/A	All negative	All negative	—
Intervention	IV penicillin 4 million U every 4 h or gentamicin 80 mg every 8 h for women with penicillin allergy	IV ampicillin 1 g every 6 h and IM gentamicin 80 mg every 8 h or IM erythromycin 500 mg every 6 h for women with penicillin allergy	IV clindamycin 600 mg every 6 h and IV cefuroxime 750 every 8 h. Then oral cefuroxime 250 mg every 12 h and clindamycin 300 mg every 6 h	IV ampicillin 1 g every 6 h and IV gentamicin 240 mg every day	IV 1500 mg ampicillin	—
Control	Placebo	No treatment	Placebo	No treatment	Placebo	—
Primary outcome	Mode of delivery	Latency, mode of delivery, chorioamnionitis	Chorioamnionitis, neonatal morbidity	Maternal infection	Neonatal sepsis	—

Data are presented as total number (n intervention/control).

GA, gestational age; *GBS*, group B *Streptococcus*; *IM*, intramuscularly; *IV*, intravenous; *N/A*, not available.

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TABLE 2
Primary and secondary outcomes of included trials

Variable	Walss Rodriguez and Navarro Castanon, 1988[14]	Cararach et al, 1998[11]	Ovalle et al, 1998[10]	Passos et al, 2012[12]	Nabhan et al, 2014[13]	Total	RR (95% CI)
Latency from admission to delivery interval, h, mean ± SD	N/A	N/A	N/A	15.0 ± 8.4 vs 14.9 ± 7.9	5.3 ± 3.5 vs 5.4 ± 3.6	—	Mean difference, −0.08 h (−0.41 to 0.26)
Latency from PROM to delivery interval, h, mean ± SD	N/A	15.4 ± 7.3 vs 16.1 ± 9.4	28.1 ± 12.9 vs 23.5 ± 11.2	17.4 ± 8.4 vs 17.3 ± 7.9	N/A	—	Mean difference, 0.46 h (−1.78 to 2.73)
Cesarean delivery	10/30 vs 8/30	N/A	10/55 vs 7/50	17/78 vs 16/83	165/820 vs 122/820	202/983 (20.5%) vs 153/983 (15.6%)	1.32 (1.09–1.60)
Chorioamnionitis	N/A	12/371 vs 17/362	1/55 vs 4/50	2/78 vs 9/83	21/820 vs 19/820	36/1324 (2.7%) vs 49/1315 (3.7%)	0.73 (0.48–1.12)
Endometritis	N/A	0/371 vs 4/362	0/55 vs 5/50	0/78 vs 2/83	5/820 vs 2/820	5/1324 (0.4%) vs 13/1315 (0.9%)	0.44 (0.18–1.10)
Induction of labor	N/A	136/371 vs 111/362	26/55 vs 23/50	48/78 vs 48/83	513/820 vs 511/820	723/1324 (54.6%) vs 693/1315 (52.7%)	1.04 (0.97–1.11)
Spontaneous labor	N/A	230/371 vs 247/362	29/55 vs 27/50	27/78 vs 35/83	N/A	289/504 (57.3%) vs 309/495 (62.4%)	0.91 (0.82–1.00)
Days of hospitalization, Mean ± SD	N/A	N/A	N/A	2.6 ± 1.7 vs 2.8 ± 1.1	N/A	—	Mean difference, −0.20 d (−0.43 to 0.26)
Breast-feeding	N/A	N/A	55/55 vs 50/50	N/A	N/A	55/55 (100%) vs 50/50 (100%)	1.00 (0.96–1.04)
Side effects	N/A	1/371 vs 0/362	0/55 vs 0/50	N/A	0/820 vs 0/820	1/1246 (0.1%) vs 0/1232 (0%)	2.93 (0.12–71.63)
NICU	N/A	N/A	0/55 vs 0/50	N/A	43/820 vs 37/820	43/875 (4.9%) vs 37/870 (4.2%)	1.16 (0.76–1.78)
Respiratory complications	N/A	10/371 vs 15/362	0/55 vs 0/50	N/A	N/A	10/426 (2.3%) vs 15/412 (3.6%)	0.65 (0.30–1.43)
Neonatal antibiotics	N/A	N/A	1/55 vs 7/50	N/A	N/A	1/55 (1.8%) vs 7/50 (14%)	0.13 (0.02–1.02)
Neonatal sepsis	N/A	1/371 vs 7/362	0/55 vs 0/50	3/78 vs 5/83	9/820 vs 7/820	13/1324 (1.0%) vs 19/1315 (1.4%)	0.69 (0.34–1.39)
Apgar <7 at 5 min	N/A	5/371 vs 5/365	0/55 vs 0/50	N/A	15/820 vs 7/820	20/1246 (1.6%) vs 12/1235 (1.0%)	1.66 (0.81–3.37)
Perinatal death	N/A	2/371 vs 2/362	0/55 vs 0/50	0/78 vs 0/83	6/820 vs 2/820	8/1324 (0.6%) vs 4/1315 (0.3%)	1.98 (0.60–6.55)

Data are presented as number intervention vs number control.

CI, confidence interval; *N/A*, not available; *neonatal antibiotics*, number of neonates who required antibiotic; *NICU*, admission to neonatal intensive care unit; *PROM*, premature rupture of membranes; *RR*, relative risk.

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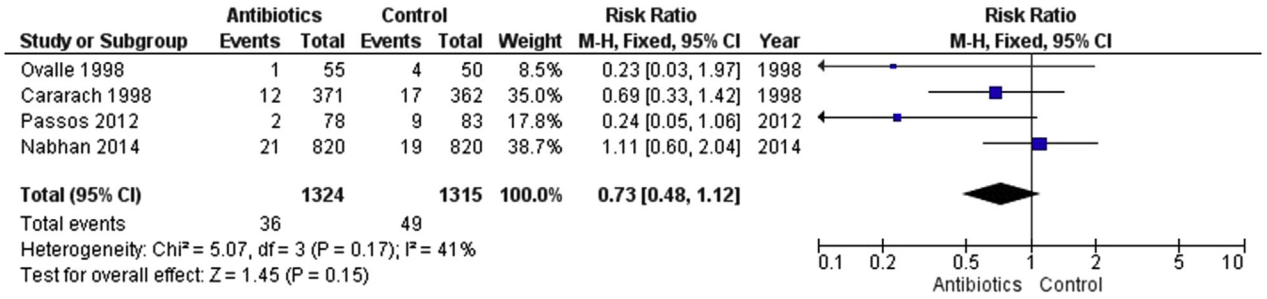
FIGURE 3
Forest plot for chorioamnionitis



CI, confidence interval.

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Most studies had a low risk of bias in allocation concealment and selective reporting by the Cochrane Collaboration's tool. Two of the 5 studies were double blind (Figure 2).

The characteristics of the 5 included trials are summarized in Table 1. Of the 2699 women, 1354 (50.1%) were randomized to the antibiotics group, whereas 1345 (49.9%) were randomized to the control group. Three of the 5 studies used a placebo as the control.

Table 2 show the primary and secondary outcomes. Given some heterogenicity among studies, random-effect models were used. There was no significant difference in latency from admission to delivery and from PROM to delivery between the 2 groups. Women who received antibiotics had the same rate of chorioamnionitis (2.7% vs 3.7%; RR, 0.73; 95% CI, 0.48−1.12), endometritis (0.4% vs 0.9%; RR, 0.44; 95% CI, 0.18−1.10), and neonatal sepsis (1.0% vs 1.4%; RR, 0.69; 95% CI, 0.34−1.39) (Table 2 and Figures 3-5).

There were no differences in all of the secondary outcomes except for the rate of cesarean delivery, which was higher in the antibiotics group compared with the controls (20.5% vs 15.6%; RR, 1.32; 95% CI, 1.09−1.60) (Table 2). Only one study reported data about septicemia, placental abruption, cord prolapse, cerebral abnormality, and cerebral palsy; however, they found no case in each groups about these outcomes.[10]

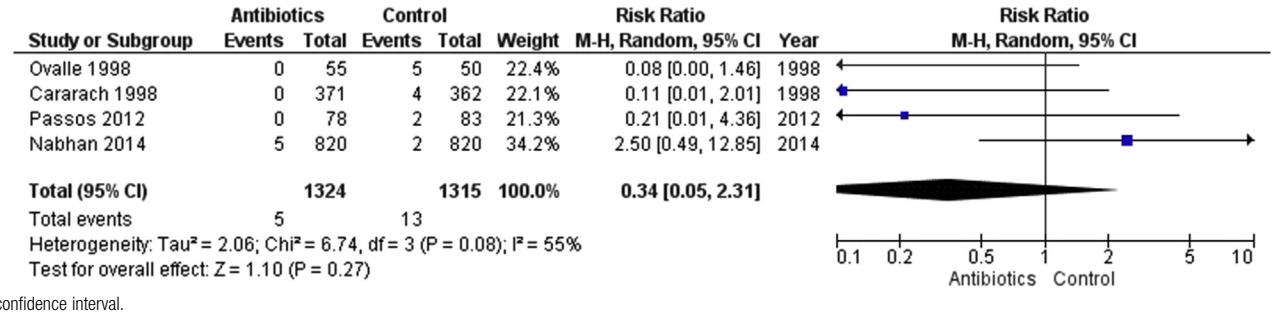
In the subgroup analysis, women with latency longer than 12 hours, who received antibiotics, had a lower rate of chorioamnionitis (2.9% vs 6.1%; RR, 0.49; 95% CI, 0.27−0.91) and endometritis (0% vs 2.2%; RR, 0.12; 95% CI, 0.02−0.62) compared with the control group. No significant difference was found in the other outcomes (Table 3 and Figures 6-8).

Conclusion

This metaanalysis of the 5 RCTs evaluating the efficacy of prophylaxis antibiotic treatment in women with term or near-term PROM shows that antibiotics treatment is not associated with the prevention of maternal chorioamnionitis or endometritis or neonatal sepsis. In the overall analysis, an increase in cesarean delivery was seen in the antibiotics group. A significant decrease in maternal chorioamnionitis and endometritis was found in the subgroup analysis of the women with latency longer than 12 hours, with no effect on the cesarean delivery rates.

Benefits of antibiotics in term or near-term PROM depend greatly on latency and so on the timing and length of induction. It has been shown that the

FIGURE 4
Forest plot for endometritis



CI, confidence interval.

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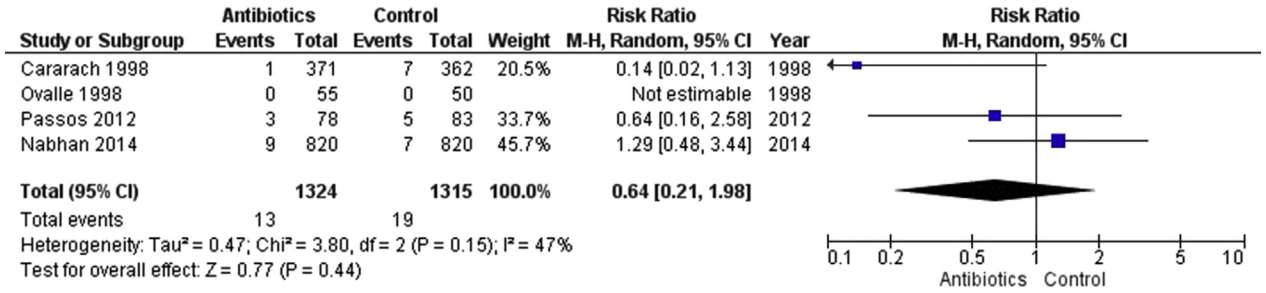
FIGURE 5
Forest plot for neonatal sepsis



CI, confidence interval.

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TABLE 3
Subgroup analysis for women with latency longer than 12 h

Variable	Cararach et al, 1998[11]	Ovalle et al, 1998[10]	Passos et al, 2012[12]	Total	RR (95% CI)
Cesarean delivery	N/A	10/55 vs 7/50	17/78 vs 16/83	27/133 (20.3%) vs 23/133 (17.3%)	1.18 (0.72–1.95)
Chorioamnionitis	12/371 vs 17/362	1/55 vs 4/50	2/78 vs 9/83	15/504 (2.9%) vs 30/495 (6.1%)	0.49 (0.27–0.91)
Endometritis	0/371 vs 4/362	0/55 vs 5/50	0/78 vs 2/83	0/504 (0%) vs 11/495 (2.2%)	0.12 (0.02–0.62)
Induction of labor	136/371 vs 111/362	26/55 vs 23/50	48/78 vs 48/83	210/504 (41.7%) vs 182/495 (36.8%)	1.14 (0.98–1.33)
Spontaneous labor	230/371 vs 247/362	29/55 vs 27/50	27/78 vs 35/83	289/504 (57.3%) vs 309/495 (62.4%)	0.91 (0.82–1.00)
Days of hospitalization, mean ± SD	N/A	N/A	2.6±1.7 vs 2.8±1.1	N/A	Mean difference, −0.20 days (−0.43 to 0.26)
Breast-feeding	N/A	55/55 vs 50/50	N/A	55/55 (100%) vs 50/50 (100%)	1.00 (0.96–1.04)
Side effects	1/371 vs 0/362	0/55 vs 0/50	N/A	1/426 (0.2%) vs 0/412 (0%)	2.93 (0.12–71.63)
NICU	N/A	0/55 vs 0/50	N/A	0/55 (0%) vs 0/50 (0%)	N/E
Respiratory complications	10/371 vs 15/362	0/55 vs 0/50	N/A	10/426 (2.3%) vs 15/412 (3.6%)	0.65 (0.30–1.43)
Neonatal antibiotics	N/A	1/55 vs 7/50	N/A	1/55 (1.8%) vs 7/50 (14%)	0.13 (0.02–1.02)
Neonatal sepsis	1/371 vs 7/362	0/55 vs 0/50	3/78 vs 5/83	4/504 (0.8%) vs 12/495 (2.4%)	0.34 (0.11–1.04)
Apgar <7	5/371 vs 5/365	0/55 vs 0/50	N/A	5/426 (1.1%) vs 5/415 (1.2%)	0.98 (0.29–3.37)
Perinatal death	2/371 vs 2/362	0/55 vs 0/50	0/78 vs 0/83	2/504 (0.4%) vs 2/495 (0.4%)	0.98 (0.29–3.37)

Data are presented as number intervention vs number control.

CI, confidence interval; *N/A*, not available; *N/E*, not applicable; *Neonatal antibiotics*, number of neonates who required antibiotic; *NICU*, admission to neonatal intensive care unit; *RR*, relative risk.

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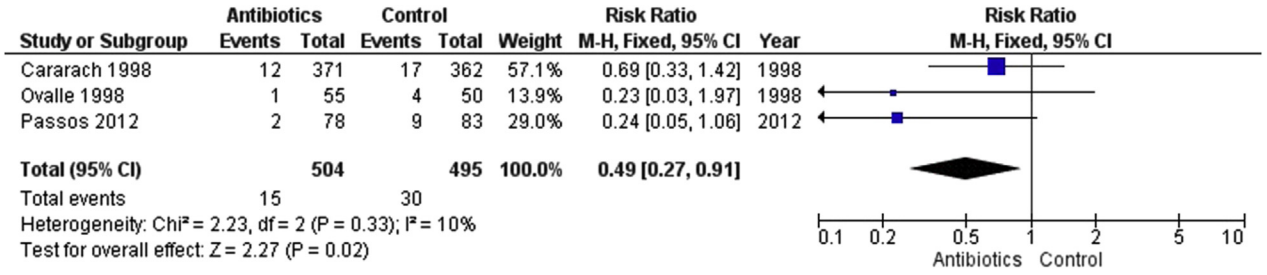
FIGURE 6
Forest plot of subgroup analysis for chorioamnionitis



CI, confidence interval.

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longer the latency between term or near-term PROM and delivery, the higher is the maternal and perinatal infectious risk. In fact, rates of chorioamnionitis and endometritis are increased 2.3-fold, with latency of more than 12 hours compared with shorter latency.[6]

Clinical examples help understand the role of prophylactic antibiotics for term or near-term PROM. A woman with term or near-term PROM and breech presentation, who immediately receives a cesarean delivery, will probably not benefit from prophylactic antibiotics just for the PROM. Conversely, a woman with a closed and long cervix presenting many hours after term or near-term PROM with a vertex presentation needing induction may have maternal and perinatal benefits from prophylactic antibiotics.

Analyzing our metaanalysis data according to length of latency, it can be seen that in term or near-term PROM, longer latency is associated with higher rates of maternal chorioamnionitis and endometritis, as well as neonatal sepsis, if no prophylactic antibiotics are given (Figure 9, A). Instead, if prophylactic antibiotics are given, these rates of maternal and neonatal infection tend to remain similar, regardless of length of latency (Figure 9, B). Clinically, these data also reinforce the recommendation for induction as soon as feasible after term or near-term PROM.

Preventing chorioamnionitis in women with term or near-term PROM may have further benefits. In fact, clinical or histological chorioamnionitis has been associated with cerebral palsy,[15] so clinical strategies to prevent or reduce rates of chorioamnionitis could potentially lead to a reduction in possible neurologic long-term consequences.

The increased rate in cesarean observed in the overall analysis, but not in the subgroup analysis, is of unclear explanation and significance. However, women with chorioamnionitis have been reported to have higher rates of CD,[16] which contradicts an association between prophylactic antibiotics and rates of CD. Rates of cesarean delivery in our metaanalysis were 20.5% in the antibiotics group and 15.6% in the control group, rates that are lower than current US cesarean rates.[17] Given these facts, it is possible that the association between prophylactic antibiotics and cesarean delivery in the overall analysis was a chance finding.

Another metaanalysis evaluated the efficacy of antibiotic prophylaxis in term or near-term PROM.[18] However, this review did not include all currently available RCTs. It showed that the use of antibiotics in PROM at term or near term was associated with a significant reduction in endometritis but not in chorioamnionitis and neonatal sepsis.

One of the strengths of our study is the inclusion of only RCTs on antibiotic prophylaxis in women with term or near-term PROM. Furthermore, no prior metaanalysis is up to date and comprehensive in terms of included studies, and the number of women

FIGURE 7
Forest plot of subgroup analysis for endometritis

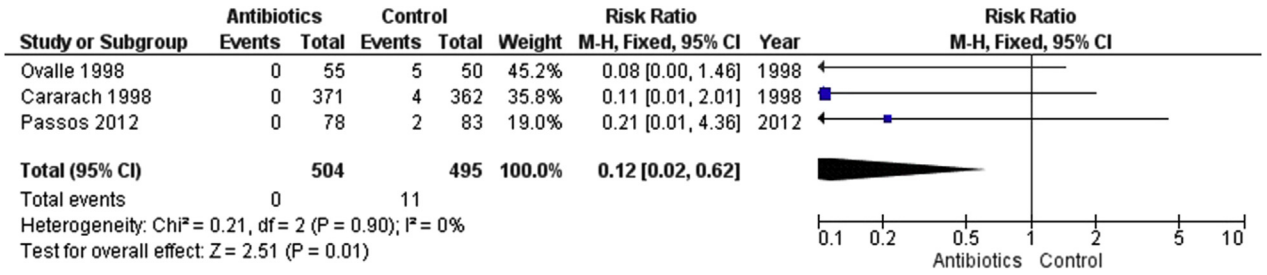

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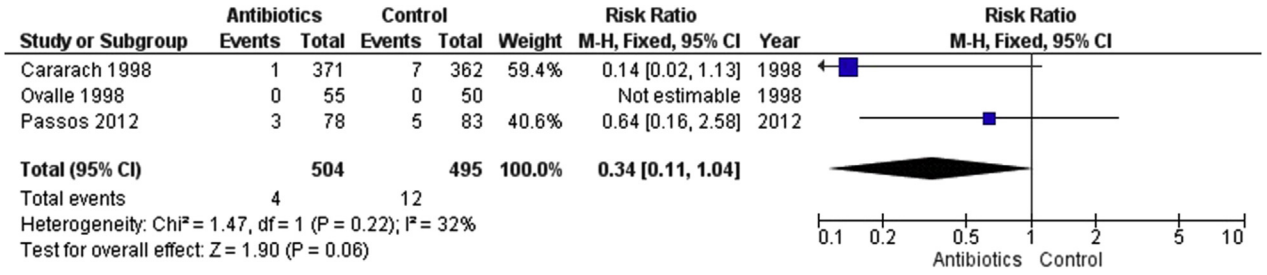
FIGURE 8
Forest plot of subgroup analysis for neonatal sepsis



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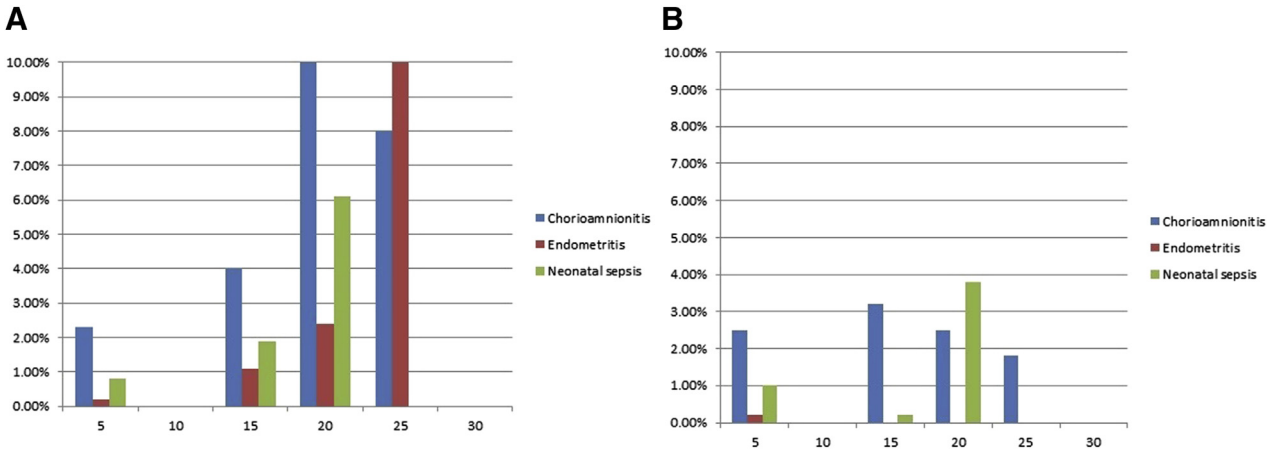
included in our analysis is the highest among all metaanalyses available. Potential publication bias was assessed by a visual inspection of the funnel plot, and a symmetric plot suggested no publication bias (Figure 10).

Limitations of our study are inherent to the limitations of the included RCTs. Only one[10] of the included studies had a low risk of bias in all items according to the Cochrane's risk of bias tool. It appears that the study by Nabhan et al[13] provided results that were somewhat different from the other studies for the main outcomes. This is probably because the investigators had the shortest latency from admission to delivery, only about 5 hours in both group (Table 2). With a short latency, the effect of antibiotics may not be apparent.

Clearly there were similarities among the studies, apart from inclusion criteria, patient population, etc. For example, in all included studies, in the absence of regular uterine contractions, oxytocin was given intravenously for induction of labor. We cannot exclude unreported differences in management among the 5 included studies, given they were published over a long time frame (1988−2014) and in 5 different countries on 3 different continents. On the other hand, this increases the external validity of the metaanalysis. Although no included study was restricted to only group B *Streptococcus* (GBS)-positive women, older studies did not specify GBS status. Our data can be used predominantly for women at 37 weeks or longer; there were no women included at less than 36 weeks.

Our metaanalysis shows that antibiotic prophylaxis in women with term or near-term PROM is not associated with benefits in the overall analysis but is associated with significant decreases of 51% in chorioamnionitis and 88% in endometritis in women with latency longer than 12 hours. When a patient presents with term PROM and it is predicted that the length of latency may be long (eg, nulliparous woman with a closed and long cervix), from a practical clinical perspective, consideration may

FIGURE 9
Incidence of chorioamnionitis, endometritis, and neonatal sepsis in length of latency

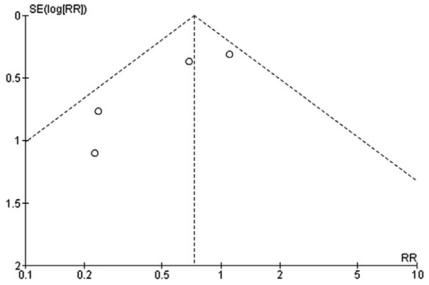


The x-axis indicates the length of latency in hours, and the y-axis indicates the incidence, in percentage, of infection. **A**, Women who received placebo or no treatment. **B**, Women in the antibiotic prophylaxis group.

CI, confidence interval.

Saccone. Antibiotic prophylaxis for term or near-term premature rupture of membranes. Am J Obstet Gynecol 2015.

FIGURE 10
Funnel plot for assessing publication bias



CI, confidence interval.

Saccone. Antibiotic prophylaxis for term or near-term premature rupture of membranes. Am J Obstet Gynecol 2015.

be given to starting prophylactic antibiotics to decrease chorioamnionitis and endometritis. Further research is needed to better predict the length of latency in term PROM and to evaluate the role of antibiotics. ■

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