Antibiotics for prelabour rupture of membranes at or near term (Review)

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[Intervention Review]

Antibiotics for prelabour rupture of membranes at or near term

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ABSTRACT

Background

Prelabour rupture of the membranes at or near term (term PROM) increases the risk of infection for the woman and her baby. The routine use of antibiotics for women at the time of term PROM may reduce this risk. However, due to increasing problems with bacterial resistance and the risk of maternal anaphylaxis with antibiotic use, it is important to assess the evidence addressing risks and benefits in order to ensure judicious use of antibiotics. This review was undertaken to assess the balance of risks and benefits to the mother and infant of antibiotic prophylaxis for prelabour rupture of the membranes at or near term.

Objectives

To assess the effects of antibiotics administered prophylactically to women with prelabour rupture of the membranes at 36 weeks or beyond, on maternal, fetal and neonatal outcomes.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (September 2008).

Selection criteria

All randomised trials which compared outcomes for women and infants when antibiotics were administered prophylactically for prelabour rupture of the membranes at or near term, with outcomes for controls (placebo or no treatment).

Data collection and analysis

Two authors independently extracted the data and assessed trial quality. Additional data were received from the investigators of included trials.

Main results

The results of two trials, involving a total of 838 women, are included in this review. The use of antibiotics resulted in a statistically significant reduction in maternal infectious morbidity (chorioamnionitis or endometritis): (risk ratio (RR) 0.43; 95% confidence interval (CI) 0.23 to 0.82); (risk difference (RD) -4%; 95% CI -7% to -1%); (number needed to treat (NNT) 25; 95% CI 14 to100).

No statistically significant differences were shown for outcomes of neonatal morbidity. However, one study of 105 women showed a reduction in neonatal length of stay (mean difference -0.90; 95% CI -1.34 to -0.46).

Authors' conclusions

No clear practice recommendations can be drawn from the results of this review on this clinically important question, related to a paucity of reliable data. Further well-designed randomised controlled trials are needed to assess the effects of routine use of maternal antibiotics for women with prelabour rupture of the membranes at or near term.

PLAIN LANGUAGE SUMMARY

Antibiotics for prelabour rupture of membranes at or near term

Giving pregnant women antibiotics when their membranes rupture at or near term without the onset of labour may reduce the risk of infections for the women. More research is needed on the safety and impact of the antibiotics on their babies. Sometimes the membranes (creating a bag of liquid around the unborn baby) break when the baby is due without the onset of regular uterine contractions. This is called PROM (prelabour rupture of membranes). When this happens, there is a risk of infection entering the womb (uterus) and affecting the mother and her baby. Most of the women spontaneously start regular uterine contractions within 24 hours, although some do not. The women are often given antibiotics to prevent infection but there are concerns about possible adverse effects of antibiotic use. The other main management strategy is to induce labour with oxytocin.

The review of trials found that routine antibiotics for term PROM reduced the risk of infection of the uterus for the pregnant woman. There was not enough strong evidence about other outcomes, including infections and complications for the baby. Only two trials involving a total of 838 women with PROM were identified. The conclusions from this review are limited by the small numbers of women enrolled in the identified trials and the low rate of maternal infection in the control groups. There is insufficient information in this review to assess possible adverse effects from the use of antibiotics for women or their infants.

BACKGROUND

Approximately eight per cent of women at term experience spontaneous rupture of the membranes prior to the onset of labour (Cammu 1990), referred to in this review as term PROM (term prelabour rupture of the membranes). Although for the majority of women, labour will start spontaneously within 24 hours following term PROM, up to four per cent will not experience spontaneous onset of labour within seven days. Although traditionally, 'term' is defined as gestations of 37 to 41 weeks inclusive, for the purposes of this review, infants born at 36 weeks gestation have been included in the definition of term PROM as neonatal outcomes at these gestations are similar to those of gestations greater than 36 weeks (Neerhoff 1999; Marshall 2002).

The reasons for term PROM are not clearly understood. However, subclinical ascending infection is thought to play a role and has been detected in up to one third of women with term PROM (Romero 1992). Despite the antibacterial properties of amniotic fluid, there is an increased risk of infection for the woman and her infant following term PROM (Newton 1993). Therefore, the routine use of antibiotics for women at the time of term PROM may reduce the risk of infection for the woman and her baby. Neonatal infections in the term population are rare occurrences (two to four per cent) but have the potential for causing mortality or serious morbidity. (including the need for neonatal intensive care and mechanical ventilation).

Induction of labour is another strategy intended to reduce infectious morbidity associated with term PROM. There is some evidence that planned management (usually by induction) reduces the risk of some infectious maternal morbidity and the number of infants going to neonatal intensive care (Dare 2006). On the basis of this evidence clinicians may offer prompt induction with oxytocin for term PROM and may consider that prelabour antibiotics are not indicated. Others utilise a policy of delayed induction of labour or expectant management (awaiting spontaneous onset of labour) (Hannah 1996). It is in these situations that prelabour antibiotics may be beneficial. However, due to increasing problems with bacterial resistance (Lin 1999) and the risk of rare but potentially life threatening risk of maternal anaphylaxis with antibiotic use (Heim 1991), it is important to ensure judicious use of antibiotics.

This review aims to address the balance of risks and benefits to the mother and infant of antibiotic prophylaxis for prelabour rupture of the membranes at or near term. The review also aims to explore

differential effects of antibiotics and induction of labour.

Although Group B Streptococcus (GBS) is the most common cause of serious neonatal infection in the first seven days of life, this review does not address the role of intrapartum antibiotic GBS prophylaxis as this is a separate clinical question from prelabour antibiotic usage. The role of intrapartum antibiotic prophylaxis for GBS is addressed in another Cochrane review (Smaill 1996).

OBJECTIVES

To assess the effects of antibiotics administered prophylactically to women with prelabour rupture of the membranes at 36 weeks or beyond, on maternal, fetal and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials which compared outcomes for women and infants when antibiotics were administered prophylactically for prelabour rupture of the membranes at or near term, with outcomes for controls (placebo or no treatment).

Types of participants

Women with spontaneous rupture of the fetal membranes prior to the onset of regular uterine contractions at gestational age 36 weeks or beyond.

Types of interventions

Any antibiotics, administered as prophylaxis, by any route, to women at gestational age 36 weeks or beyond, with prelabour rupture of the membranes.

Types of outcome measures

Maternal outcomes:

- suspected or proven chorioamnionitis;
- endometritis;
- caesarean section;
- operative delivery;
- internal fetal monitoring;
- epidural analgesia;
- post partum haemorrhage;
- post partum pyrexia;
- post partum septicaemia;
- wound infection;
- adverse drug reactions;
- post partum antibiotic usage;
- breastfeeding on discharge from hospital;
- length of hospital stay;
- fetal death;
- fetal death unrelated to congenital abnormality.

Neonatal outcomes:

- neonatal early onset sepsis (definite and probable);
- neonatal sepsis (definite and probable);
- neonatal meningitis;
- neonatal pneumonia;
- Apgar score < 7 at five minutes;
- admission to neonatal special care nursery;
- admission to neonatal intensive care nursery;
- use of antibiotics;
- use of mechanical ventilation;
- length of hospital stay;
- neonatal death;
- neonatal death unrelated to congenital abnormality;
- perinatal mortality;
- perinatal mortality unrelated to congenital abnormality;

Cost-effectiveness.

A priori sub group analyses:

- nulliparae;
- early induction of labour (less than 12 hours from rupture of membranes);
- late induction (at 12 hours or greater from rupture of membranes);
- delivery within 18 hours of rupture of membranes;
- delivery within 24 hours of rupture of membranes.

Outcome definitions

Suspected or proven chorioamnionitis: uterine infection prior to delivery of the baby diagnosed on clinical signs, including pyrexia with or without a positive culture result or haematological signs of infection.
Maternal pyrexia: maternal temperature of 38 degrees centigrade or higher.
Endometritis: clinical signs of uterine infection following labour and delivery .
Post partum septicaemia: maternal positive blood culture in the presence of pyrexia following delivery of the baby.
Neonatal sepsis: definite or probable infection in the neonatal period (up to 28 days of life).

Early onset sepsis: definite or probable infection within the first seven days of life.
Definite infection: positive culture from a normally sterile site.
Probable infection: clinical signs and blood count suggestive of infection and a possible causative organism identified (ie gastric aspirate, urine antigen).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (September 2008).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.
Searches carried out in the previous version of the review are listed in Appendix 1.

Data collection and analysis

Two authors independently assessed trial quality and extracted data who then compared and resolved differences. We conducted quality assessment according to the methods described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We considered six domains of trial quality for assessing risk of bias: (1) sequence generation (2) allocation concealment (3) Blinding of participants, personnel and outcome assessors (4) incomplete outcome data (5) selective outcome reporting (6) other sources of bias. The quality assessment was based on the systematic assessment for the opportunity for each of these biases to arise. Thus, the review authors judged for each trial whether each criterion was met. Studies were judged 'YES' for meeting the domain criteria and hence having a low risk of bias, 'NO' for not meeting the domain criteria and hence a high risk of bias, or 'UNCLEAR' if adequate explanation for a domain was not reported. Additional information on study methods and additional data for prespecified maternal and neonatal outcomes were sought from the authors of included studies. Additional information on method of random allocation and some additional outcome data were received from the authors. (For further details please see table of Characteristics of included studies).
Meta-analysis was undertaken using a fixed-effect model and results are presented using relative risk (RR), risk difference (RD) and number needed to treat (NNT) (where appropriate) for categorical data, and mean difference (MD) for variables measured on a continuous scale. All results are presented with 95% confidence intervals (CI).
Heterogeneity was assessed by visual inspection of the outcomes tables and by using two statistics (H and I^2 test) of heterogeneity (Higgins 2008). Where statistical heterogeneity was found, the authors looked for an explanation. A statistical synthesis of the results using a random-effects model was undertaken where it was thought studies with heterogeneous results were comparable.
Subgroup analyses were planned as follows:

- High quality trials versus low quality (high quality trials are defined as those considered to have a low risk of bias overall according to the quality assessment as detailed above);
- The use of antibiotics with expectant management versus active management (i.e a policy for early induction of labour).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Six trials were identified for possible inclusion in this review. Four trials were excluded: Lebherz 1963 was excluded as the antibiotic (tetracycline) is now contraindicated in pregnancy and Brelje 1966 and Gordon 1974 because a quasi-random method of allocation was employed. A further trial was excluded because additional information on methods of randomisation and allocation to treatment was not available (Walss Rodriguez 1988). See 'Characteristics of excluded studies'.
Two randomised trials are included in this review (Cararach 1998; Ovalle 1998). The population of women in the included trials were similar. The gestation of women enrolled was 37 to 42 weeks in Cararach 1998 and 36 weeks or greater for Ovalle 1998. Both

trials excluded women with multiple pregnancy and major obstetric complications and had stipulated criteria for diagnosis of membrane rupture.
Some differences were apparent in management protocols and types of antibiotics used.

Management protocols

Both trials had systematic approaches to routine maternal cervicovaginal cultures on admission. Ovalle 1998 also conducted amniocentesis for culture of amniotic fluid. Induction of labour with intravenous oxytocin was undertaken in both trials, however, the timing of induction differed. Cararach 1998 employed a policy of induction of labour for all women not in labour after 12 hours of membrane rupture. In Ovalle 1998 induction of labour was undertaken within 24 hours of membrane rupture and in an unknown proportion an earlier threshold was used (details are unclear). Both trials employed management protocols which involved attempts to minimise vaginal examinations. Routine antibiotic prophylaxis at the time of caesarean section was given in Cararach 1998 but inconsistently in Ovalle 1998. Neither trial included a description of a policy for prevention of neonatal early onset Group B streptococcal disease. Ovalle 1998 administered routine antibiotics to neonates of mothers with clinical chorioamnionitis or positive maternal admission cultures (Group B streptococcal, haemophilus influenzae or chlamydia trachomatis). Cararach 1998 did not describe the use of neonatal antibiotics for maternal risk factors.

Antibiotics

Cararach 1998 used intravenous ampicillin (or intramuscular erythromycin for women with penicillin allergy) with intramuscular gentamicin and Ovalle 1998 used intravenous cefuroxime and clindamycin for 48 hours then oral cefuroxime and clindamycin for a further 24 hours.

Outcomes

The outcomes of maternal infection (chorioamnionitis and endometritis) and neonatal infection were assessed in both included trials. Maternal infection (chorioamnionitis, endometritis) was well defined in both trials. Cararach 1998 diagnosed neonatal early onset sepsis according to well defined clinical criteria, with or without positive blood culture, within 72 hours of birth. Ovalle 1998 did not define neonatal sepsis, but reported no cases of neonatal morbidity in the trial. Long term neonatal outcomes were not assessed in either trial.
For further details please see table of 'Characteristics of included studies'.

Risk of bias in included studies

The included trials were of fair quality. Random allocation was undertaken in the included trials using a computer generated list of random numbers, however, allocation to treatment was not concealed in either trial. The intervention was blinded in Ovalle 1998 with the use of a placebo for the control group; no placebo was used in Cararach 1998. Cararach 1998 undertook blinded assessment of neonatal outcomes with disclosure of allocation only in cases of neonatal sepsis. Both trials reported an intention to treat analysis and complete follow up.

Effects of interventions

The results of two trials comparing the use of antibiotics with no use of antibiotics for women with term PROM (Cararach 1998; Ovalle 1998), involving a total of 838 women, are included in this review.

Maternal outcomes:

The use of antibiotics resulted in a statistically significant reduction in endometritis (risk ratio (RR) 0.09; 95% confidence interval (CI) 0.01 to 0.73); no difference was shown in maternal infectious morbidity (chorioamnionitis and/or endometritis) using a random-effects model (RR 0.34; 95% CI 0.08 to 1.47; heterogeneity I^2 = 54%).
No statistically significant differences were shown for any other reported outcomes as follows: chorioamnionitis (RR 0.60; 95% CI 0.30 to 1.18), maternal adverse drug reaction (RR 2.93; 95% CI 0.12 to 71.63), maternal length of hospital stay (MD 0.10 days; 95% CI -0.45 to 0.65).

Neonatal outcomes:

One trial (Ovalle 1998) showed a statistically significant reduction in the neonatal length of hospital stay (MD -0.90; 95% CI -1.34 to -0.46).
No statistically significant differences were shown for any of the following outcomes:
Apgar scores < 7 at five minutes (RR 0.98; 95% CI 0.28 to 3.34), neonatal early onset infection (RR 0.14; 95% CI 0.02 to 1.13), neonatal early onset infection - positive blood culture (RR 0.16; 95% CI 0.02 to 1.34), pneumonia (RR 0.33; 95% CI 0.01 to 7.96), meningitis (RR 0.33; 95% CI 0.03 to 3.11), neonatal mechanical ventilation (RR 0.73; 95% CI 0.16 to 3.25) or perinatal mortality (RR 0.98; 95% CI 0.14 to 6.89).
Due to insufficient data, we were unable to undertake subgroup analyses to explore the effects of trial quality or the use of antibiotics with expectant management.

DISCUSSION

Because of a paucity of reliable information, this review does not provide sufficient evidence to justify the routine use of antibiotics prior to the onset of labour for women with term PROM.

The conclusions from this review are limited by small numbers of women enrolled and rare event rates for important outcomes. The two included trials used management policies involving the administration of intravenous antibiotics for approximately 48 hours and delayed induction with oxytocin (up to 24 hours). It is therefore not possible to generalise these findings to other antibiotic schedules (eg oral administration) or women undergoing expectant management.

Although antibiotics for women with term prelabour rupture of membranes was shown to reduce maternal infectious morbidity (chorioamnionitis and/or endometritis), given the low rate of maternal infection in the control population (approximately seven per cent), it does not seem justifiable to expose all women with term PROM to antibiotics when treatment can be restricted to those who develop clinical indications for antibiotic treatment. There is insufficient information in this review to assess possible adverse effects from the use of antibiotics for women or their infants.

There were no clear neonatal benefits demonstrated for any of the prespecified outcomes.

It is possible that the modest benefit for maternal infectious morbidity seen within these trials might be greater in circumstances where the duration of membrane rupture was more prolonged (related to either a policy of expectant management or a delay in induction greater than 24 hours). Because the important clinical outcomes associated with this clinical scenario are so rare, this question can only be resolved by very large placebo controlled trials.

AUTHORS' CONCLUSIONS

Implications for practice

Until more reliable evidence is available indicating overall benefit from prelabour prophylactic antibiotics for term PROM it would seem prudent that their routine use be avoided.

Implications for research

Further well designed randomised controlled trials are needed to assess the effects of routine use of prelabour antibiotics (particularly oral administration) for women with term PROM, for those women being managed expectantly or with a policy of delayed induction. Such trials should utilise blinding of the intervention and need to be adequately sized to address clinically important maternal and neonatal outcomes and include a cost analysis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cararach 1998

Methods	Multicentre randomised trial (11 hospitals in Spain).
Participants	733 women. Inclusion criteria: GA 36 weeks or more, singleton pregnancy, MR duration less than 12 hrs and absence of uterine contractions. Exclusion criteria: Fetal death or anomaly, placenta praevia, abruptio placentae, fetal distress, chorioamnionitis, indication for elective CS, allergy to penicillin and erythromycin.
Interventions	Intervention: Antibiotics on admission following vaginal and endocervical culture. IV ampicillin 1g every 6 hrs and IM gentamicin 80mgs every 8 hrs or IM erythromycin 500mgs every 6 hrs for women with penicillin allergy. Controls: No placebo Admission cultures as for intervention group.
Outcomes	Maternal: Chorioamnionitis, endometritis. Neonatal: Respiratory complications (including pneumonia, idiopathic respiratory distress, transient tachypnoea) early onset sepsis (<72 hrs of birth), Apgar Score at 1 and 5 minutes. Data were requested and received for: maternal adverse drug reaction, neonatal mechanical ventilation, perinatal death. Maternal adverse drug reaction.
Notes	Management of all women enrolled: Single vaginal examination until initiation of labour. Vaginal and endocervical culture on admission. Induction of labour with IV oxytocin after 12 hrs of MR in the absence of regular uterine contractions. Routine antibiotic prophylaxis for women undergoing CS.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation method according to a "Randomisation list in each participating centre".
Allocation concealment?	No	

Cararach 1998 (*Continued*)

Blinding? All outcomes	Unclear	Blinding of intervention: No. Blinding of outcome assessment: Neonatal outcomes only. Unblinding in cases of neonatal sepsis.
Incomplete outcome data addressed? All outcomes	Yes	complete follow up

Ovalle 1998

Methods	Single centre randomised trial.
Participants	105 women. Inclusion criteria: GA 37-42 weeks, singleton pregnancy, duration of MR less than 12 hrs, no labour. Exclusion criteria: previous CS, malpresentation, fetal distress, fetal malformation, chorioamnionitis, antibiotics given within 30 days.
Interventions	Intervention: Antibiotics on admission following cervicovaginal and amniotic fluid culture. IV clindamycin 600 mg every 6 hrs and IV cefuroxime 750mgs every 8 hrs for 48 hrs then oral cefuroxime 250mgs every 12 hrs and clindamycin 300mgs every 6 hrs for a further 24 hrs. Control: Placebo following admission cultures. No details provided.
Outcomes	Maternal: Chorioamnionitis, endometritis. Neonatal: Apgar score <7 at 5 mins, neonatal morbidity. Dates were requested and received for: neonatal sepsis, pneumonia, meningitis, neonatal mechanical ventilation, admission to special care nursery, maternal and neonatal length of stay, perinatal death, maternal adverse drug reaction.
Notes	Management of all women enrolled: No digital vaginal examination until active labour. Cervicovaginal culture and culture of amniotic fluid by amniocentesis on admission. Induction of labour with IV oxytocin within 24 hrs of MR if no labour. Antibiotic prophylaxis given to some women undergoing CS. Neonatal antibiotics routinely given when chorioamnionitis present or positive maternal admission cultures.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomization by "consecutive numbers according to a pre-established allocation code"

Ovalle 1998 (*Continued*)

Allocation concealment?	No	
Blinding? All outcomes	Unclear	Blinding of intervention: yes, placebo controlled Blinding of outcome assesment: yes
Incomplete outcome data addressed? All outcomes	Yes	Complete follow up

CS: caesarean section
GA : gestational age
hrs: hours
IM: intramuscular
IV: intravenous
mins: minutes
MR: membrane rupture

Characteristics of excluded studies *[ordered by study ID]*

Brelje 1966	Quasi-random allocation used.
Gordon 1974	Quasi-random allocation used.
Lebherz 1963	Antibiotic used no longer recommended for use in pregnancy.
Walss Rodriguez 1988	Further information on method of randomisation and allocation to treatment was requested but is not yet available.

DATA AND ANALYSES

Comparison 1. Any antibiotic compared with no antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chorioamnionitis	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.30, 1.18]
2 Endometritis	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.73]
3 Maternal infectious morbidity (chorioamnionitis and/or endometritis)	2	838	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.08, 1.47]
4 Maternal adverse drug reaction	2	838	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.63]
5 Apgar score <7 at 5 minutes	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.28, 3.34]
6 Admission to neonatal intensive care	1	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Neonatal early onset sepsis	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.13]
8 Neonatal early onset sepsis - positive blood culture	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.34]
9 Neonatal pneumonia	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
10 Neonatal meningitis	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.11]
11 Neonatal mechanical ventilation	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.16, 3.25]
12 Perinatal mortality	2	838	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.89]
13 Neonatal length of hospital stay	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.34, -0.46]
14 Maternal length of hospital stay	1	105	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.45, 0.65]

Analysis 1.1. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 1 Chorioamnionitis.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

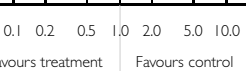
Outcome: 1 Chorioamnionitis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	12/371	17/362		80.4 %	0.69 [0.33, 1.42]
Ovalle 1998	1/55	4/50		19.6 %	0.23 [0.03, 1.97]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.60 [0.30, 1.18]**

Total events: 13 (Treatment), 21 (Control)

Heterogeneity: Chi^2 = 0.92, df = 1 (P = 0.34); I^2 =0.0%

Test for overall effect: Z = 1.49 (P = 0.14)



Analysis 1.2. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 2 Endometritis.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

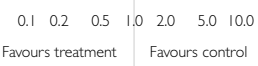
Outcome: 2 Endometritis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	0/371	4/362		44.2 %	0.11 [0.01, 2.01]
Ovalle 1998	0/55	5/50		55.8 %	0.08 [0.00, 1.46]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.09 [0.01, 0.73]**

Total events: 0 (Treatment), 9 (Control)

Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 2.27 (P = 0.023)



Analysis 1.3. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 3 Maternal infectious morbidity (chorioamnionitis and/or endometritis).

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

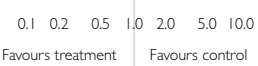
Outcome: 3 Maternal infectious morbidity (chorioamnionitis and/or endometritis)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cararach 1998	12/371	21/362		68.4 %	0.56 [0.28, 1.12]
Ovalle 1998	1/55	8/50		31.6 %	0.11 [0.01, 0.88]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.34 [0.08, 1.47]**

Total events: 13 (Treatment), 29 (Control)

Heterogeneity: Tau^2 = 0.70; Chi^2 = 2.16, df = 1 (P = 0.14); I^2 =54%

Test for overall effect: Z = 1.45 (P = 0.15)



Analysis 1.4. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 4 Maternal adverse drug reaction.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

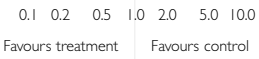
Outcome: 4 Maternal adverse drug reaction

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	1/371	0/362		100.0 %	2.93 [0.12, 71.63]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**2.93 [0.12, 71.63]**

Total events: 1 (Treatment), 0 (Control)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.66 (P = 0.51)



Analysis 1.5. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 5 Apgar score <7 at 5 minutes.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

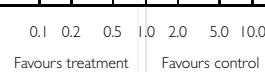
Outcome: 5 Apgar score <7 at 5 minutes

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	5/371	5/362		100.0 %	0.98 [0.28, 3.34]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.98 [0.28, 3.34]**

Total events: 5 (Treatment), 5 (Control)

Heterogeneity: Chi^2 = 0.00, df = 0 (P<0.00001); I^2 =100%

Test for overall effect: Z = 0.04 (P = 0.97)



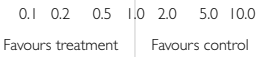
Analysis 1.6. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 6 Admission to neonatal intensive care.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

Outcome: 6 Admission to neonatal intensive care

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**55**	**50**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



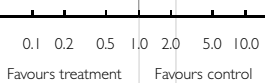
Analysis 1.7. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 7 Neonatal early onset sepsis.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

Outcome: 7 Neonatal early onset sepsis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	1/371	7/362		100.0 %	0.14 [0.02, 1.13]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.14 [0.02, 1.13]**
Total events: 1 (Treatment), 7 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 1.85 (P = 0.065)					



Analysis 1.8. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 8 Neonatal early onset sepsis - positive blood culture.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

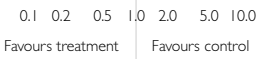
Outcome: 8 Neonatal early onset sepsis - positive blood culture

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	1/371	6/362		100.0 %	0.16 [0.02, 1.34]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.16 [0.02, 1.34]**

Total events: 1 (Treatment), 6 (Control)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.69 (P = 0.092)



Analysis 1.9. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 9 Neonatal pneumonia.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

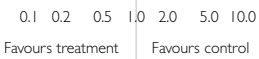
Outcome: 9 Neonatal pneumonia

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	0/371	1/362		100.0 %	0.33 [0.01, 7.96]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.33 [0.01, 7.96]**

Total events: 0 (Treatment), 1 (Control)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.69 (P = 0.49)



Analysis 1.10. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 10 Neonatal meningitis.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

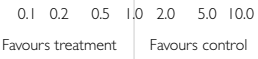
Outcome: 10 Neonatal meningitis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	1/371	3/362		100.0 %	0.33 [0.03, 3.11]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.33 [0.03, 3.11]**

Total events: 1 (Treatment), 3 (Control)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.97 (P = 0.33)



Analysis 1.11. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 11 Neonatal mechanical ventilation.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

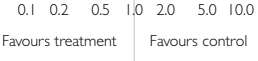
Outcome: 11 Neonatal mechanical ventilation

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	3/371	4/362		100.0 %	0.73 [0.16, 3.25]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.73 [0.16, 3.25]**

Total events: 3 (Treatment), 4 (Control)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.41 (P = 0.68)



Analysis 1.12. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 12 Perinatal mortality.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

Outcome: 12 Perinatal mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cararach 1998	2/371	2/362		100.0 %	0.98 [0.14, 6.89]
Ovalle 1998	0/55	0/50		0.0 %	0.0 [0.0, 0.0]
Total (95% CI)	**426**	**412**		**100.0 %**	**0.98 [0.14, 6.89]**

Total events: 2 (Treatment), 2 (Control)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.02 (P = 0.98)

Analysis 1.13. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 13 Neonatal length of hospital stay.

Review: Antibiotics for prelabour rupture of membranes at or near term

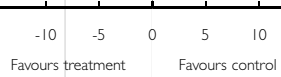
Comparison: 1 Any antibiotic compared with no antibiotic

Outcome: 13 Neonatal length of hospital stay

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ovalle 1998	55	3 (1.21)	50	3.9 (1.1)		100.0 %	-0.90 [-1.34, -0.46]
Total (95% CI)	**55**		**50**			**100.0 %**	**-0.90 [-1.34, -0.46]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.99 (P = 0.000065)

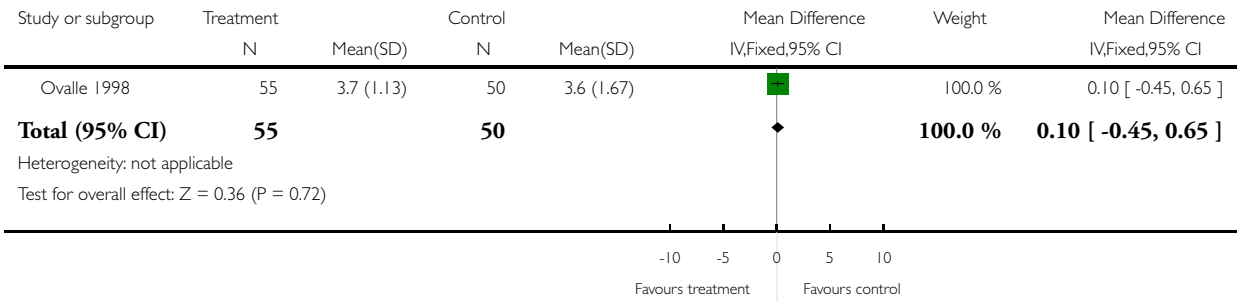


Analysis 1.14. Comparison 1 Any antibiotic compared with no antibiotic, Outcome 14 Maternal length of hospital stay.

Review: Antibiotics for prelabour rupture of membranes at or near term

Comparison: 1 Any antibiotic compared with no antibiotic

Outcome: 14 Maternal length of hospital stay



APPENDICES

Appendix 1. Searches carried out in the previous version

The authors conducted a systematic literature search which included electronic databases: the Cochrane Controlled Trials Register (*The Cochrane Library* 2001, Issue 4) and MEDLINE (1965 to 2001), using MeSH headings: pregnancy and childbirth, infant-newborn and the search terms: term, chorioamnionitis, membrane* , rupture*, prelabour, prelabor, ROM, antibiotic*, neonat*, sepsis, early onset sepsis.

The authors also contacted recognised experts and cross referenced relevant material.

WHAT'S NEW

Last assessed as up-to-date: 22 December 2008.

23 December 2008	New search has been performed	Search updated. No new trials identified. Two studies previously awaiting classification have been excluded (Gordon 1974; Walss Rodriguez 1988).

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 3, 2002

28 August 2008	Amended	Converted to new review format.
30 September 2005	New search has been performed	Search updated. No new trials identified.

CONTRIBUTIONS OF AUTHORS

Vicki Flenady and James King worked as equal partners in the production of this review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Centre for Clinical Studies - Mater Hospital, South Brisbane, Queensland, Australia.
- J P Kelly Research Foundation, Mater Hospital, South Brisbane, Queensland, Australia.
- Department of Perinatal Medicine, Royal Women's Hospital, Melbourne, Victoria, Australia.

External sources

- Department of Health and Ageing, Commonwealth Government, Canberra, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Bacterial Infections [*prevention & control]; Fetal Membranes, Premature Rupture [*complications]; Infant, Newborn; Risk Assessment; Treatment Outcome

MeSH check words

Female; Humans; Pregnancy