Antibiotic regimens for management of intra-amniotic infection (Review)

Chapman E, Reveiz L, Illanes E, Bonfill Cosp X

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 12

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Antibiotic regimens for management of intra-amniotic infection

Evelina Chapman[1], Ludovic Reveiz[2], Eduardo Illanes[3], Xavier Bonfill Cosp[4]

[1]Free time independent Cochrane reviewer, Tucumàn, Argentina. [2]Knowledge Management, Bioethics and Research Department, Pan American Health Organization, Washington, DC, USA. [3]Servicio de Psiquiatría Complejo Hospitalario Barros Luco/Facultad de Medicina Escuela de Psicología Universidad Mayor Santiago, Santiago, Chile. [4]Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP) - Universitat Autònoma de Barcelona, Barcelona, Spain

Contact address: Ludovic Reveiz, Knowledge Management, Bioethics and Research Department, Pan American Health Organization, Washington, DC, USA. mmreveiz@hotmail.com. lreveiz@yahoo.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 12, 2014.
Review content assessed as up-to-date: 18 September 2014.

Citation: Chapman E, Reveiz L, Illanes E, Bonfill Cosp X. Antibiotic regimens for management of intra-amniotic infection. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD010976. DOI: 10.1002/14651858.CD010976.pub2.

ABSTRACT

Background

Chorioamnionitis is a common infection that affects both mother and infant. Infant complications associated with chorioamnionitis include early neonatal sepsis, pneumonia, and meningitis. Chorioamnionitis can also result in maternal morbidity such as pelvic infection and septic shock.

Clinical chorioamnionitis is estimated to occur in 1% to 2% of term births and in 5% to 10% of preterm births; histologic chorioamnionitis is found in nearly 20% of term births and in 50% of preterm births. Women with chorioamnionitis have a two to three times higher risk for cesarean delivery and a three to four times greater risk for endomyometritis, wound infection, pelvic abscess, bacteremia, and postpartum hemorrhage.

Objectives

To assess the effects of administering antibiotic regimens for intra-amniotic infection on maternal and perinatal morbidity and mortality and on infection-related complications.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 October 2014), CENTRAL, MEDLINE, Embase, LILACS, and the WHO ICTRP (September 2014). We also searched reference lists of retrieved studies and contacted experts in the field.

Selection criteria

Randomized controlled trials (RCTs) that included women who experienced intra-amniotic infection. Trials were included if they compared antibiotic treatment with placebo or no treatment (if applicable), treatment with different antibiotic regimens, or timing of antibiotic therapy (intrapartum and/or postpartum). Therefore, this review assesses trials evaluating intrapartum antibiotics, intrapartum and postpartum antibiotic regimens, and postpartum antibiotics. Diagnosis of intra-amniotic infection was based on standard criteria (clinical/test), and no limit was placed on gestational age.

Data collection and analysis

Two review authors independently assessed trials for inclusion and trial quality. Two review authors independently extracted data and checked them for accuracy. We assessed the quality of the evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach and included a 'Summary of findings' table.

Main results

Our prespecified primary outcomes were maternal and neonatal mortality, maternal and neonatal severe infection, and duration of maternal and neonatal hospital stay.

We included 11 studies (involving 1296 women) and assessed them as having low to moderate risk of bias - mainly because allocation concealment methods were not adequately reported, most studies were open, and outcome reporting was incomplete. The quality of the evidence was low to very low for most outcomes, as per the GRADE approach. The following antibiotics were assessed in the included trials: ampicillin, ampicillin/sulbactam, gentamicin, clindamycin, and cefotetan.

During labor: meta-analysis of two studies found no clear differences in rates of neonatal sepsis (163 neonates; risk ratio (RR) 1.07, 95% confidence interval (CI) 0.40 to 2.86; I^2 = 9%; low quality of evidence), treatment failure (endometritis) (163 participants; RR 0.86, 95% CI 0.27 to 2.70; I^2 = 0%; low quality of evidence), and postpartum hemorrhage (RR 1.39, 95% CI 0.76 to 2.56; I^2 = 0%; low quality of evidence) when two different dosages/regimens of gentamicin were assessed. No clear differences between groups were found for any reported maternal or neonatal outcomes. The review did not identify data for a comparison of antibiotics versus no treatment/placebo.

Postpartum: meta-analysis of two studies that evaluated use of antibiotics versus placebo after vaginal delivery showed no significant differences between groups in rates of treatment failure or postpartum endometritis. No significant differences were found in rates of neonatal death and postpartum endometritis when use of antibiotics was compared with no treatment. Four trials assessing two different dosages/regimens of gentamicin or dual-agent therapy versus triple-agent therapy, or comparing antibiotics, found no significant differences in most reported neonatal or maternal outcomes; the duration of hospital stay showed a difference in favor of the group of women who received short-duration antibiotics (one study, 292 women; mean difference (MD) -0.90 days, 95% CI -1.64 to -0.16; moderate quality of evidence).

*Intrapartum versus postpartum: o*ne small study (45 women) evaluating use of ampicillin/gentamicin during intrapartum versus immediate postpartum treatment found significant differences favoring the intrapartum group in the mean number of days of maternal postpartum hospital stay (one trial, 45 women; MD -1.00 days, 95% CI -1.94 to - 0.06; very low quality of evidence) and the mean number of neonatal hospital stay days (one trial, 45 neonates; MD -1.90 days, 95% CI -3.91 to -0.49; very low quality of evidence). Although no significant differences were found in the rate of maternal bacteremia or early neonatal sepsis, for the outcome of neonatal pneumonia or sepsis we observed a significant difference favoring intrapartum treatment (one trial, 45 neonates; RR 0.06, 95% CI 0.00 to 0.95; very low quality of evidence).

Authors' conclusions

This review included 11 studies (having low to moderate risk of bias). The quality of the evidence was low to very low for most outcomes, as per the GRADE approach. Only one outcome (duration of hospital stay) was considered to provide moderate quality of evidence when antibiotics (short duration) were compared with antibiotics (long duration) during postpartum management of intra-amniotic infection. Our main reasons for downgrading the quality of evidence were limitations in study design or execution (risk of bias), imprecision, and inconsistency of results.

Currently, limited evidence is available to reveal the most appropriate antimicrobial regimen for the treatment of patients with intra-amniotic infection; whether antibiotics should be continued during the postpartum period; and which antibiotic regimen or what treatment duration should be used. Also, no evidence was found on adverse effects of the intervention (not reported in any of the included studies). One small RCT showed that use of antibiotics during the intrapartum period is superior to their use during the postpartum period in reducing the number of days of maternal and neonatal hospital stay.

PLAIN LANGUAGE SUMMARY

Using antibiotics to treat intra-amniotic infection in pregnant women

Review question: Cochrane authors reviewed available evidence from randomized controlled trials on the use of antibiotics for the treatment of pregnant women with intra-amniotic infection (chorioamnionitis).

Background: chorioamnionitis is a common occurrence among pregnant women that affects both mother and baby and usually results in referral to hospital. It is an infection of the fetal membranes, amniotic fluid, and placenta that can cause complications for the newborn infant including whole body inflammation or sepsis, pneumonia, and meningitis. Chorioamnionitis can also result in health issues for the mother such as pelvic infection, sepsis, postpartum hemorrhage, and increased risk for cesarean delivery of the infant. Risk factors for developing chorioamnionitis include active labor for a long time, extended duration of rupture of membranes and internal monitoring, meconium staining of amniotic fluid, and a large number of digital vaginal examinations. Treatment for patients with intra-amniotic infection usually consists of antibiotics that can be administered during birth or immediately afterward. Currently, information is insufficient to suggest the most appropriate treatment regimen, which antibiotic regimen should be used, and whether antibiotics should be continued during the period immediately following birth and for what duration.

Study characteristics: a total of 11 studies were identified with 1296 women; most studies were conducted in the USA. Four studies evaluated the use of antibiotics before the birth (antepartum); six studies evaluated the use of antibiotics after birth (postpartum); and one compared antibiotic administration both before and after birth.

Quality of the evidence: the quality of the evidence was ranked low to very low, mainly because many studies had methodological limitations with outcome results based on limited numbers of trials and included participants that could be pooled.

Key results: based on the findings of one study, treatment during labor was found to be more effective than treatment after labor; however this finding relates only to maternal and neonatal length of hospital stay and to neonatal severe infection. No evidence indicated that a higher dose of antibiotics before birth was superior to a lower dose. Immediately following birth, no evidence showed that different types of antibiotics or longer or shorter treatment duration improved the health of the mother and her newborn. All women who participated in the postpartum trials received antibiotics before the time of birth. Therefore insufficient information was available from randomized controlled trials to reveal the most appropriate regimen of antibiotics for the treatment of patients with intra-amniotic infection, whether antibiotics should be continued during the postpartum period, and which antibiotic regimen should be used and for what duration. None of the included studies reported information related to adverse effects of the intervention.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotics versus antibiotics in labor for management of intra-amniotic infection

Population: women in labor with management of intra-amniotic infection
Settings: hospitals in the USA
Intervention: antibiotics vs antibiotics in labor

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotics versus antibiotics				
Maternal death	See comment	See comment	Not estimable	38 (1 study)	See comment	Comparing daily gentamicin versus 8-hour gentamicin. Outcome was reported with no events
Neonatal deaths	**Study population**		**RR 1.39** (0.24 to 8.06)	133 (1 study)	⊕◯◯◯ **Very low**[a,b]	Comparing dual-agent therapy versus triple-agent therapy.
	31 per 1000	**43 per 1000** (7 to 252)				
	Moderate					
	31 per 1000	**43 per 1000** (7 to 250)				
Neonatal sepsis	**Study population**		**RR 1.07** (0.4 to 2.86)	163 (2 studies)	⊕⊕◯◯ **Low**[a]	Comparing daily gentamicin versus 8-hour gentamicin.
	84 per 1000	**90 per 1000** (34 to 241)				
	Moderate					

	141 per 1000	**151 per 1000** (56 to 403)				
Respiratory distress syndrome	**Study population**		**RR 1.69** (0.42 to 6.78)	125 (1 study)	⊕⊕◯◯ **Low**[a]	Comparing daily gentamicin versus 8-hour gentamicin.
	48 per 1000	**80 per 1000** (20 to 323)				
	Moderate					
	48 per 1000	**81 per 1000** (20 to 325)				
Maternal postpartum hospital stay (days)		Mean maternal postpartum hospital stay (days) in the intervention groups was **0 higher** (0.43 lower to 0.43 higher)		125 (1 study)	⊕⊕◯◯ **Low**[c]	Comparing daily gentamicin versus 8-hour gentamicin.
Postpartum readmission for endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Treatment failure (endometritis)	**Study population**		**RR 0.86** (0.27 to 2.7)	163 (2 studies)	⊕⊕◯◯ **Low**[a]	Comparing daily gentamicin versus 8-hour gentamicin.
	72 per 1000	**62 per 1000** (20 to 195)				
	Moderate					

	65 per 1000	**56 per 1000** (18 to 176)	

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Wide confidence interval crossing the line of no effect, few events, and small sample size.
[b]One study with design limitations.
[c]Wide confidence interval crossing the line of no effect and small sample size.

BACKGROUND

Description of the condition

Chorioamnionitis is a "histopathologic finding of inflammation of the amnion and/or the chorion" (Fahey 2008) that usually results from an infection of the fetal membranes, amniotic fluid, and placenta and/or decidua during pregnancy; it poses a significant risk to infant and maternal morbidity and mortality. The clinical definition of chorioamnionitis can vary, but the condition is best characterized as maternal fever (100.4 degrees Fahrenheit) that is not attributable to another cause along with at least one of the following symptoms: maternal tachycardia, fetal tachycardia, uterine tenderness, maternal leukocytosis (white blood cell count greater than 15,000 mL), and amniotic fluid with a foul odor (Fishman 2012). It can also be referred to as intra-amniotic infection (IAI), amnionitis, and amniotic fluid infection (Incerpi 2010; Tita 2010). Chorioamnionitis can be defined clinically or histologically. Clinical chorioamnionitis is estimated to occur in 1% to 2% of term births and in 5% to 10% of preterm births; histologic chorioamnionitis is found in nearly 20% of term births and in 50% of preterm births (Incerpi 2010).

Few diagnostic tests are specific and sensitive, as well as safe for mother and infant; therefore, chorioamnionitis is diagnosed primarily through assessment of clinical signs and symptoms. A culture of the amniotic fluid obtained from an amniocentesis is the reference standard for diagnosis, but 48 hours is required to obtain test results, and evidence of reduced maternal or neonatal morbidity is insufficient. Blood cultures and vaginal swabs are other diagnostic tests for chorioamnionitis, but supportive evidence for both is limited, and some recommendations suggest that vaginal swabs should not be used in cases of preterm prelabor rupture of membranes (Czikk 2011).

As with clinical chorioamnionitis, the case definition of histologic chorioamnionitis varies between studies (Holzman 2007), but it can generally be defined as acute inflammatory changes in the placenta membrane roll and chorionic plate (Yoon 2001). Diagnosis is made on the basis of microscopic examination of placental and chorioamnionic specimens (Tita 2010).

Chorioamnionitis is most frequently caused by bacteria ascending from the lower genital tract; it is predominantly seen in instances of rupture of the membrane, but it can occur in intact membranes (Fahey 2008). This infection can also be caused by bloodborne or transplacental infection, and by transuterine infection from invasive procedures such as amniocentesis or chorionic villus sampling, but these routes tend to be reported less commonly (Edwards 2005; Fahey 2008).

Chorioamnionitis is generally a polymicrobial infection; most cases have two detectable pathogens, but the infection can be caused by viral and, in rare instances, fungal agents (Czikk 2011). Organisms commonly found in amniotic fluid are *Mycoplasma hominis* and *Ureaplasma urealyticum* (Tita 2010), but other pathogens include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, anaerobic Gram-negative bacilli such as *Bacteroides* and *Gardnerella vaginalis*, *Escherichia coli*, and anaerobic streptococci and streptococci group B (Czikk 2011; Edwards 2005).

The differential diagnosis of chorioamnionitis includes epidural-associated fever and other extrauterine and non-infectious conditions. An epidural-associated fever may be considered for intrapartum women with epidurals and a low-grade fever but without maternal or fetal tachycardia or other clinical symptoms. Fever and abdominal pain are symptoms of extrauterine infections including urinary tract infection, influenza, appendicitis, and pneumonia. Abdominal pain without a fever may indicate a non-infectious condition including thrombophlebitis, round ligament pain, colitis, connective tissue disorder, and placental abruption (Tita 2010).

Risk factors for developing chorioamnionitis include being in active labor for a long time, extended duration of rupture of membranes and internal monitoring (Newton 1989), meconium staining of amniotic fluid, a large number of digital vaginal examinations (Seaward 2005), nulliparity, African American ethnicity, smoking and alcohol or drug abuse, epidural anesthesia, bacterial vaginosis, and colonization with group B streptococcus or *Ureaplasma* bacterium (Tita 2010).

Preventing chorioamnionitis is better than treatment, and some interventions have been shown to reduce the incidence of chorioamnionitis (Gibbs 2004). A 53% reduction in maternal morbidity due to chorioamnionitis and endometritis was seen in women with term pregnancies receiving an active management of labor program compared with traditional management (López-Zeno 1992). For at-term pregnancies complicated by prelabor rupture of the membranes (PROM), management by immediate oxytocin induction compared with conservative management led to fewer cases of chorioamnionitis (Mozurkewich 1997), and for preterm pregnancies with PROM, use of broad-spectrum antibiotics showed a decrease in chorioamnionitis (Kenyon 2013).

Description of the intervention

Some aspects of the timing of antibiotic therapy (intrapartum, postpartum, or combined intrapartum and postpartum), the antibiotic regimen, and the duration of antibiotic therapy have been evaluated in individual situations but not comprehensively (Fishman 2012). A previous Cochrane review (Hopkins 2002) identified two randomized controlled trials assessing use of ampicillin and gentamicin for intrapartum treatment of women with intra-amniotic infection versus postpartum treatment and use of ampicillin/gentamicin/clindamycin versus ampicillin/gentamicin; none of the outcomes showed statistically significant differences between different interventions.

How the intervention might work

Treatment for chorioamnionitis usually consists of antibiotics that can be administered intrapartum or immediately postpartum. As the infection could be caused by a wide variety of organisms, treatment with a broad spectrum of antibiotics is needed. The typical standard of care consists of clindamycin for anaerobic and gram-positive bacteria and gentamicin for aerobic and gram-negative bacteria (Mtira 1997).

Why it is important to do this review

Chorioamnionitis is a common infection that affects both mother and infant. Infant complications associated with chorioamnionitis include early neonatal sepsis, pneumonia, meningitis (Incerpi 2010), asthma (Getahun 2010), cerebral palsy (Wu 2000), intraventricular hemorrhage (Edwards 2005), and periventricular leukomalacia (Edwards 2005; Rocha 2007). Although fetal complications are more common, chorioamnionitis can also result in maternal morbidity such as pelvic infection and septic shock (Incerpi 2010). The risk for cesarean delivery is two to three times higher in women who have chorioamnionitis and is three to four times greater for those with endomyometritis, wound infection, pelvic abscess, bacteremia, and postpartum hemorrhage (Tita 2010).

A Cochrane review was conducted 10 years ago to study the effects of maternal antibiotic regimens for intra-amniotic infection on maternal and perinatal morbidity and mortality (Hopkins 2002). This review identified two eligible studies, and conclusions were limited because of the small number of identified studies. A statistically significant difference was not seen in any of the outcomes; therefore the review authors were not able to make recommendations on timing of administration of antibiotic treatment (intrapartum vs postpartum). Additionally, no Cochrane systematic review to date has evaluated studies in which antibiotic treatment for chorioamnionitis was given during the postpartum period. Currently, information is insufficient to reveal the most appropriate antimicrobial regimen for the treatment of patients with intra-amniotic infection, whether antibiotics should be continued during the postpartum period, and which antibiotic regimen and what treatment duration should be used. This review updates the Hopkins 2002 review with new references and an expanded scope to include antibiotic regimens during the postpartum period.

OBJECTIVES

To assess the effects of administering antibiotic regimens for intra-amniotic infection on maternal and perinatal morbidity and mortality and infection-related complications.

METHODS

Criteria for considering studies for this review

Types of studies

We included all individually randomized and cluster-randomized controlled trials comparing antibiotic treatment versus placebo or no treatment. We also included trials that compared different antibiotics or regimens. Trials of intrapartum antibiotics for intra-amniotic infection and trials comparing intrapartum versus postpartum regimens were included.

We excluded studies that used inappropriate methods of randomization, as well as cross-over trials and quasi-randomized trials.

Types of participants

Women who experienced intra-amniotic infection. Diagnosis was based on standard criteria (clinical/test). No limit was placed on gestational age.

Types of interventions

Trials were included if they compared antibiotic treatment versus placebo or no treatment (if applicable), treatment with different antibiotic regimens, or timing of antibiotic therapy (intrapartum and/or postpartum). Therefore, the review included trials evaluating intrapartum antibiotics, intrapartum and postpartum antibiotic regimens, and postpartum antibiotics.

Types of outcome measures

Primary outcomes

1. Maternal and neonatal mortality.
2. Maternal and neonatal severe infection.
3. Duration of maternal and neonatal hospital stay.

Secondary outcomes

1. Need for additional antibiotic therapy.
2. Endometritis.
3. Febrile days.
4. Postpartum readmission for endometritis.
5. Failure of treatment.
6. Blood cultures and other diagnostic tests (positive findings).
7. Number of doses of antibiotic(s).
8. Infection-related complications.
9. Adverse events (eg, allergic reactions, antibiotic-associated diarrhea, development of bacterial resistance).
10. Suspension or cessation of breastfeeding.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (1 October 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE, and Embase; 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.

Each of the trials identified through the search activities described above is 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.

In addition, we searched:

1. CENTRAL (see Appendix 1); September 22, 2014;
2. MEDLINE (accessed via PubMed) (see Appendix 2); September 22, 2014;
3. Embase (accessed via Ovid) (see Appendix 3); September 23, 2014;
4. LILACS (from 1982 onwards) (see Appendix 4) (Manríquez 2008); September 22, 2014; and
5. WHO International Clinical Trials Registry Platform (ICTRP) (see Appendix 5); September 18, 2014.

Searching other resources

We also checked the reference lists of all trials identified by the above methods and tried to contact leading researchers to obtain information on additional published and unpublished trials.

We applied no language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion potential studies identified as a result of the search strategy. Disagreements were resolved through discussion or, if required, a third review author was consulted.

Data extraction and management

We designed a form on which to record extracted data. For eligible studies, two review authors extracted data using the agreed upon form. We resolved discrepancies through discussion or, if required, we consulted the third review author. We entered data into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to obtain further details. This was difficult, given that many trials were not published recently.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by consultation with a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, eg, random number table; computer random number generator);
- high risk of bias (any non-random process, eg, odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions before assignment and assessed whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (eg, telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth); or
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention was provided for a participant. We considered that studies were at low risk of bias if they were blinded, or if we judged that lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or different classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants; or
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the quantity, nature, and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, completeness of data including attrition and exclusions from analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total number of randomly assigned participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported, or was supplied by the trial authors, we planned to reinclude missing data in the analyses that we undertook; however, this was not done.

We assessed methods as:

- low risk of bias (eg, no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (eg, numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization); or
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (when not all of the study's prespecified outcomes have been reported; when one or more reported primary outcomes were not prespecified; when outcomes of interest were reported incompletely and so could not be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk of bias.

(6). Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns that we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias.

- Low risk of other bias.
- High risk of other bias.
- Unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgments about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to 1 to 6 above, we assessed the likely magnitude and direction of the bias, and whether we considered it likely to impact study findings. We explored the impact of the level of bias by undertaking sensitivity analyses (see Sensitivity analysis).

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Schunemann 2009) to assess the quality of the body of evidence as related to the following outcomes.

- Maternal and neonatal mortality.
- Maternal and neonatal severe infection.
- Duration of maternal and neonatal hospital stay.
- Need for additional antibiotic therapy.
- Endometritis.
- Postpartum readmission for endometritis.
- Failure of treatment.

GRADE profiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach is based on five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) that are used to assess the quality of the body of evidence for each outcome. Evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for

risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios with 95% confidence intervals.

Continuous data

For continuous data, we used mean differences if outcomes were measured in the same way between trials. We used standardized mean differences to combine trials that measured the same outcome while using different methods.

Unit of analysis issues

Cluster-randomized trials

Although we planned to include cluster-randomized trials in the analyses along with individually randomized trials, we did not identify any cluster-randomized trials for inclusion. However, if we identify cluster-randomized trials for inclusion in future updates of this review, we will adjust standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* based on an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we use ICCs from other sources, we will report this and will conduct sensitivity analyses to investigate the effects of variation in ICCs. If we identify both cluster-randomized trials and individually randomized trials, we plan to synthesize relevant information. We will consider it reasonable to combine the results from both ICCs if little heterogeneity is observed between study designs and if the interaction between effects of interventions and choice of the randomization unit is considered unlikely.
We will also acknowledge heterogeneity in the randomization unit and will perform a sensitivity analysis to investigate the effects of the randomization unit.

Other unit of analysis issues

Studies with multiple intervention groups were dealt with as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Each intervention arm was separately compared with another.

Dealing with missing data

For included studies, we noted levels of attrition. We tried to explore the impact of including studies with high levels of missing data on the overall assessment of treatment effect by performing sensitivity analyses.
For all outcomes, we carried out analyses, when possible, on an intention-to-treat basis, that is, we attempted to include in the analyses all participants randomly assigned to each group, and all participants were analysed in the group to which they were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each trial was the number randomly assigned minus the number of participants whose outcomes were known to be missing.

Assessment of heterogeneity

We tested for heterogeneity between trials by using T^2, I^2, and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either T^2 was greater than zero or the P value was low (less than 0.10) in the Chi^2 test for heterogeneity. We explored heterogeneity by subgroup analysis. We used the random-effects meta-analysis as an overall summary when substantial heterogeneity was found (Higgins 2011).

Assessment of reporting biases

In future updates of this review, if 10 or more studies are included in the meta-analysis, we will investigate reporting biases (such as publication bias) by using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate this.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2014). We used fixed-effect meta-analyses for combining data when it was reasonable to assume that studies were estimating the same underlying treatment effect (i.e. when trials were examining the same intervention, and the trials' populations and methods were deemed sufficiently similar). If clinical heterogeneity was sufficient to indicate that underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analyses to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. In future updates, the random-effects summary will be treated as the average range of possible treatment effects; we discussed the clinical implications of differing treatment effects between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.
When we used random-effects analyses, the results were presented as average treatment effect with 95% confidence intervals, along with estimates of T^2 and I^2 (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We planned that when we identified substantial heterogeneity, we would investigate it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We did not carry out our prespecified subgroup analyses because data were insufficient. We plan to carry out the following subgroup analyses for future updates.

1. Gestational age (preterm versus term).
2. Women who were or were not in labor.
3. Women having vaginal versus instrumental or cesarean delivery.
4. Women in whom membranes were or were not intact.
5. Study design (cluster-randomized trials versus individually randomized controlled trials).

We will restrict subgroup analyses to the primary outcomes of the review.

1. Maternal and/or neonatal mortality.
2. Maternal and/or neonatal severe infection.
3. Duration of maternal and/or neonatal hospital stay.

We will assess subgroup differences by performing interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses by quoting the Chi^2 statistic and the P value, along with the interaction test I^2 value.

Sensitivity analysis

Explicit judgments were made as to whether studies were at high risk of bias (low versus unclear or high for sequence generation, allocation concealment and blinding domains) according to the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The likely magnitude and direction of bias and its likely impact on study findings were assessed. Sensitivity analyses were not undertaken but will be carried out in future updates, if appropriate. Sensitivity analysis will be restricted to the review's primary outcomes.

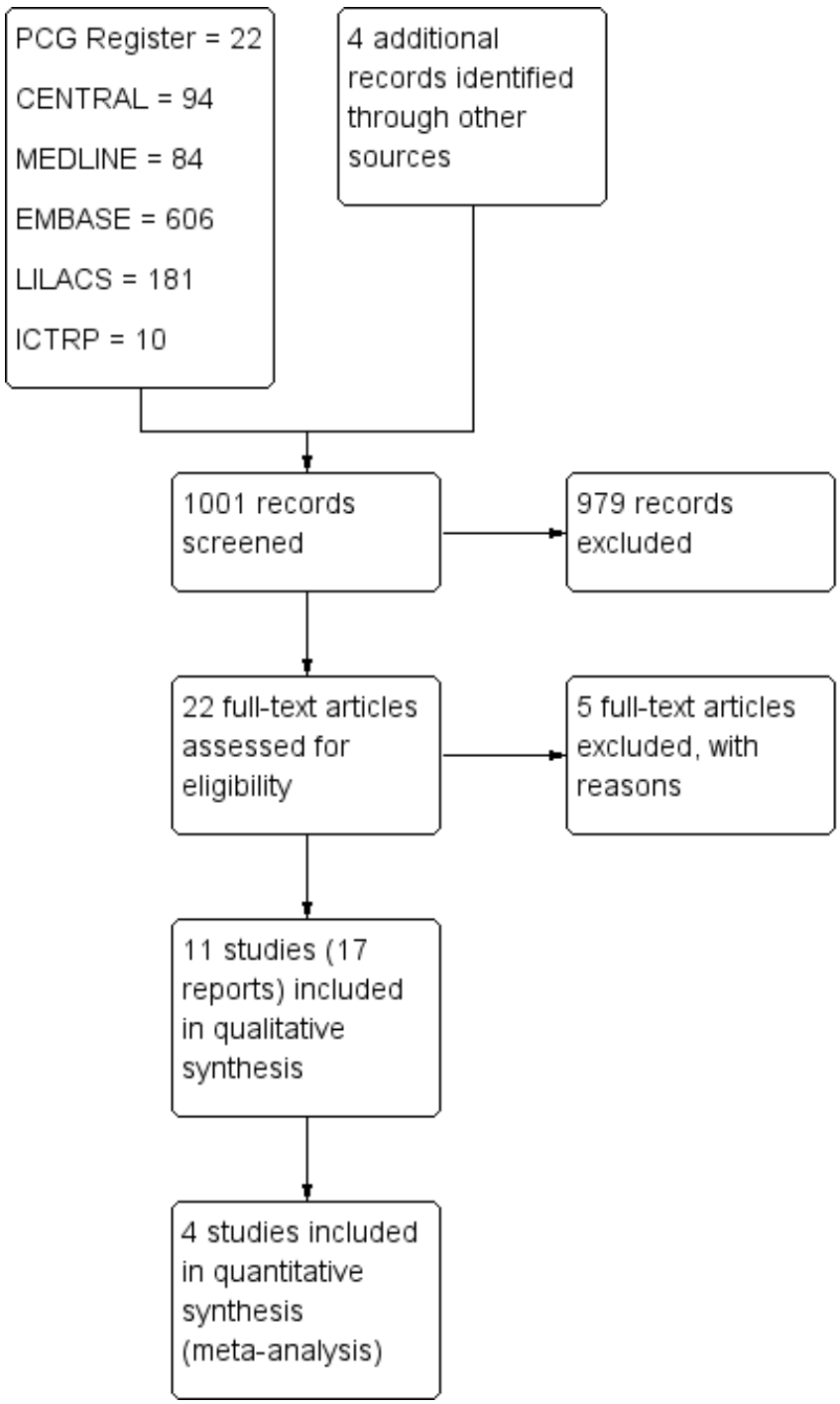
RESULTS

Description of studies

Results of the search

A search of the Cochrane Pregnancy and Childbirth Group's Register yielded 22 reports. We retrieved 94 from CENTRAL, 84 from MEDLINE, 606 from Embase, 181 from LILACS, and 10 from the WHO International Clinical Trials Registry Platform (ICTRP) (see Figure 1). An initial trawl through this list, undertaken by two review authors (LR and EC), excluded 369 references that did not comply with the inclusion criteria. We screened 24 trials: We excluded five and included 11 randomized controlled trials (RCTs) (17 reports). Two trials are ongoing (Aziz 2009; Shanks 2012).

Figure 1. Study flow diagram.



Included studies

Only one out of 11 RCTs that met the inclusion criteria was published as an abstract (Adashek 1998).

Design

All included studies were RCTs.

Settings

Most trials were conducted in the United States of America, usually by the Deparment of Obstetrics and Gynecology of an academic institution; only one study was conducted in Italy (Scalambrino 1989).

Participants

The 11 included studies provided data from a total of 1296 women. Inclusion criteria varied with respect to gestational age, labor status (active, undergoing an induction, cesarean section), maternal age, and definition of chorioamnionitis, among others. Some trials included women who required cesarean delivery (Berry 1994; Chapman 1997; Edwards 2003; Gibbs 1988; Mitra 1997; Turnquest 1998).

The main characteristics of included studies are detailed in the Characteristics of included studies table.

Interventions

During labor

Four studies compared varied regimens or doses of antibiotics versus the same or other antibiotics in labor (Locksmith 2005; Lyell 2010; Maberry 1991; Scalambrino 1989). Locksmith 2005 evaluated the use of two different doses of gentamicin. Lyell 2010 compared the effects of shorter versus longer use of gentamicin: Women in one group received a single dose of gentamicin 5 mg/kg followed by saline placebo, and those in the other group were given gentamicin 1.5 mg/kg every eight hours. In the study of Locksmith 2005, group one received 5.1 mg/kg once daily, and group two was given 80 mg every eight hours. Although the interventions were not exactly the same, data from the two studies were pooled.

Maberry 1991 assessed the effects of using dual-agent therapy (ampicillin/gentamicin) or triple-agent therapy (ampicillin/gentamicin/clindamycin). Finally Scalambrino 1989 evaluated the use of sulbactam/ampicillin versus cefotetan.

No trial was found that compared antibiotics versus no treatment or placebo during labor exclusively. In the trial of Lyell 2010, women were assigned to daily gentamicin 5 mg/kg intravenously (IV), followed by a normal saline placebo after eight hours and after 16 hours.

Postpartum

Six studies assessed the use of antibiotics during the postpartum period.

Turnquest 1998 evaluated the use of clindamycin and gentamicin versus no scheduled postoperative antibiotics in women with a clinical diagnosis of chorioamnionitis treated with ampicillin during labor and who required cesarean delivery for obstetric indications.

Two studies compared the use of antibiotics (gentamicin/clindamycin (Adashek 1998) and ampicillin/gentamicin (Berry 1994)) versus placebo after vaginal delivery.

One study evaluated the effectiveness of once-daily versus thrice-daily gentamicin/clindamycin (Mitra 1997). Two studies evaluated the effects of short versus long periods of antibiotic treatment (ampicillin/gentamicin (Edwards 2003) and cefotetan (Chapman 1997)) after delivery.

Intrapartum versus postpartum

One trial assessed the use of ampicillin/gentamicin during intrapartum versus immediate postpartum (Gibbs 1988).

Outcomes

Although most studies reported at least one prespecified primary outcome of this review, differences in reporting and definitions of outcomes were noted. For example, treatment failure was clinically defined in different ways, and adverse events were not frequently reported.

Length of follow-up

Participants were followed up until the time of discharge from the institution. Some trials reported longer periods of follow-up. Gibbs 1988 reported that four weeks after discharge, the mother was contacted by telephone or by letter and hospital records were assesssed for readmission. Lyell 2010 reported that participants were called after 10 days post discharge. Turnquest 1998 reported that all participants were scheduled to return to the postpartum clinic six weeks after hospital discharge. Mitra 1997 stated that relapse was defined as a cure with subsequent wound infection, abscess, or recurrent endometritis up to six weeks after delivery.

Berry 1994 reported that participants were given six-week postpartum clinic appointments and strict discharge instructions to return. Chapman 1997 stated that a research nurse called each woman within the first week to determine whether she had additional symptoms to report.

Funding source

Only three studies described the source of funds (Berry 1994; Edwards 2003; Lyell 2010).

Excluded studies

A total of five studies were excluded for the following reasons: inadequate randomization (strict alternation); non-RCT; inadequate reporting (outcome data not provided); very small sample size (five women randomly assigned as part of a trial with broader inclusion criteria). Reasons for exclusion are detailed in the Characteristics of excluded studies table. Ten studies were found in the ICTRP database, and two ongoing RCTs complied with inclusion criteria (Aziz 2009; Shanks 2012); no report of the study results was available in clinicaltrials.gov.

Risk of bias in included studies

Overall studies had moderate risk of bias, mainly because allocation concealment, methods of sequence generation, blinding, and selective reporting were not adequately reported. In addition, it was not clear whether follow-up was similar for the treatment groups.

Sequence generation and allocation concealment

Sequence generation

Nine RCTs adequately reported methods of generation of randomization, which was attained by using a random number table or a computer-generated random number table (Berry 1994; Chapman 1997; Edwards 2003; Locksmith 2005; Lyell 2010; Maberry 1991; Mitra 1997; Turnquest 1998) or by flipping a coin (Gibbs 1988). The other two RCTs did not report how randomization was performed.

Allocation concealment

Seven trials adequately reported how allocation concealment was maintained (Berry 1994; Chapman 1997; Edwards 2003; Locksmith 2005; Lyell 2010; Mitra 1997; Turnquest 1998). In these RCTs, allocation concealment was ensured by the use of sealed, opaque, sequentially numbered envelopes or by similar labels for placebo and antibiotic containers provided by the pharmacist (who was the only one to know assignment).

In one RCT (Gibbs 1988), although sealed envelopes were used, no further description was provided. The other three RCTs (Adashek 1998; Maberry 1991; Scalambrino 1989) did not report how allocation concealment was performed and were rated as having unclear risk of bias.

Blinding

Most of the studies were open RCTs, and no blinding of participants, clinicians, or researchers was reported. Berry 1994 conducted a "double-blind" trial in which the pharmacy labeled placebo and antibiotic containers alike. Only when failure of treatment occurred did the pharmacy reveal treatment or placebo status. In the double-blind trial conducted by Lyell 2010, the primary outcome was determined on the basis of chart review and follow-up phone calls by a single provider who was blinded to group allocation. In another trial (Locksmith 2005), reviewers who assessed outcomes were blinded to assignment of women to treatment groups.

Incomplete outcome data

Six studies adequately reported losses to follow-up (Berry 1994; Chapman 1997; Edwards 2003; Locksmith 2005; Lyell 2010; Maberry 1991). However, it is important to note that different lengths of follow-up were reported. Adverse outcomes and complications frequently were not defined and were not reported in a standardized way. Five trials were assessed as having 'unclear' risk of attrition bias (Adashek 1998; Gibbs 1988; Mitra 1997; Scalambrino 1989; Turnquest 1998).

Selective reporting

Most RCTs were judged as having unclear risk of reporting bias, mainly because information was insufficient to permit a judgment. One study (Lyell 2010) was assessed as having low risk of bias; this study was registered at clinicaltrials.gov and reported prespecified outcomes.

Other potential sources of bias

Seven studies were assessed as having low risk of bias (Berry 1994; Chapman 1997; Edwards 2003; Locksmith 2005; Lyell 2010; Maberry 1991; Turnquest 1998).

Three studies were assessed as having unclear risk of bias. In one study, baseline characteristics of the groups were not reported (Adashek 1998). In the Gibbs 1988 study, the intrapartum group was significantly older than the postpartum group (P = 0.03). Finally, Mitra 1997 reported that 65.7% of participants in the conventional arm were delivered by cesarean section, whereas 52.6% of women in the experimental arm had a cesarean delivery (P value 0.03).

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotics versus antibiotics in labor for management of intra-amniotic infection; **Summary of findings 2** Antibiotics versus no treatment during postpartum period for management of intra-amniotic infection; **Summary of findings 3** Antibiotics versus placebo during postpartum period for management of intra-amniotic infection; **Summary of findings 4** Antibiotic versus antibiotics during postpartum period for management of intra-amniotic infection; **Summary of findings 5** Antibiotics (short duration) compared with antibiotics (long duration) postpartum for management of intra-amniotic infection; **Summary of findings 6** Intrapartum compared with postpartum treatment

During labor

Comparison 1. Antibiotic versus no treatment

No studies comparing antibiotics versus no treatment were identified.

Comparison 2. Antibiotic versus placebo

No studies comparing antibiotics versus placebo were identified.

Comparison 3. Antibiotics versus antibiotics

Four studies compared varied regimens or doses of antibiotics versus the same or other antibiotics in labor.

Primary outcomes

Meta-analysis of two studies (Locksmith 2005; Lyell 2010) found no significant differences in the rate of neonatal sepsis (163 neonates; risk ratio (RR) 1.07, 95% confidence interval (CI) 0.40 to 2.86; I^2 = 9%; Analysis 3.8) when two different dosages/regimens of gentamicin were assessed.

No statistically significant difference in maternal postpartum stay was found in individual studies when groups of treatment were compared (one study, 125 women; mean difference (MD) 0.00, 95% CI -0.43 to 0.43; Analysis 3.6). No maternal deaths were reported in any treatment groups.

In another study (Maberry 1991), which evaluated the effects of dual-agent therapy (ampicillin/gentamicin) or triple-agent therapy (ampicillin/gentamicin/clindamycin), no significant differences were found between groups in rates of neonatal sepsis (one trial, 133 neonates; RR 0.93, 95% CI 0.06 to 14.52; Analysis 3.16) or neonatal death (one trial, 133 neonates; RR 1.39, 95% CI 0.24 to 8.06; Analysis 3.17).

Finally Scalambrino 1989 reported no maternal deaths when evaluating the use of sulbactam/ampicillin versus cefotetan (Analysis 3.12).

Secondary outcomes

Meta-analysis of two studies (Locksmith 2005; Lyell 2010) showed no significant differences in rates of treatment failure (endometritis) (RR 0.86, 95% CI 0.27 to 2.70; two studies; 163 participants (Analysis 3.1) or postpartum hemorrhage (RR 1.39, 95% CI 0.76 to 2.56; 163 participants; Analysis 3.4) when two different dosages/regimens of gentamicin were assessed.

No statistically significant differences were found in other maternal or neonatal outcomes in individual studies: initial successful response to antibiotics (one trial, 125 women; RR 1.05, 95% CI 0.94 to 1.17; Analysis 3.2); maximum maternal temperature (one trial, 125 women; MD 0.40, 95% CI -0.45 to 1.25; Analysis 3.3); blood transfusion (one trial, 125 women; RR 0.76, 95% CI 0.18 to 3.27; Analysis 3.5); histologic chorioamnionitis (one trial, 125 women; RR 0.92, 95% CI 0.63 to 1.33; Analysis 3.7); respiratory distress syndrome (one trial, 125 neonates; RR 1.69, 95% CI 0.42 to 6.78; Analysis 3.9); and neonatal antibiotics days (one trial, 125 neonates; MD 0.20, 95% CI -0.37 to 0.77; Analysis 3.10) when treatment groups were compared.

In another study (Maberry 1991) evaluating the effects of dual-agent therapy (ampicillin/gentamicin) versus triple-agent therapy (ampicillin/gentamicin/clindamycin), no significant differences were found between groups in rates of postpartum endometritis (one trial, 133 women; RR 1.86, 95% CI 0.67 to 5.14; Analysis 3.13) (vaginal: one trial, 73 women; RR 9.63, 95% CI 0.55 to 167.95; Analysis 3.14; or cesarean section: one trial, 60 women; RR 1, 95% CI 0.32 to 3.10; Analysis 3.15); intraventricular hemorrhage (one trial, 133 neonates; RR 4.64, 95% CI 0.23 to 94.90; Analysis 3.18); respiratory distress syndrome (one trial, 133 neonates; RR 1.11, 95% CI 0.36 to 3.47; Analysis 3.19), or neonatal seizures (one trial, 133 neonates; RR 0.93, 95% CI 0.06 to 14.52; Analysis 3.20).

Postpartum

Comparison 4. Antibiotic versus no treatment

Only one study (Turnquest 1998) evaluated use of clindamycin and gentamicin versus no scheduled postoperative antibiotics.

Primary outcomes

No significant differences among groups were found in rates of neonatal sepsis (one trial, 116 neonates; RR 1.11, 95% CI 0.23 to 5.27; Analysis 4.3) and neonatal death (one trial, 116 neonates; RR 3.32, 95% CI 0.14 to 79.88; Analysis 4.4).

Secondary outcomes

No significant differences among groups were found in rates of postpartum endometritis (one trial, 116 women; RR 1.48, 95% CI 0.68 to 3.24; Analysis 4.1); wound infection (one trial, 116 women; RR 0.37, 95% CI 0.04 to 3.45; Analysis 4.2); and transient tachypnea (one trial, 116 neonates; RR 0.83, 95% CI 0.19 to 3.55; Analysis 4.5).

Comparison 5. Antibiotic versus placebo

Primary outcomes

One study evaluating the use of antibiotics versus placebo after vaginal delivery (Berry 1994) reported no cases of sepsis (Analysis 5.4).

Secondary outcomes

Meta-analysis of two studies (Adashek 1998; Berry 1994) that evaluated use of antibiotics versus placebo after vaginal delivery showed no differences in the rate of treatment failure (two trials, 288 women; RR 0.97, 95% CI 0.14 to 6.77; I^2 = not estimable; Analysis 5.1). Both studies reported that no women in either allocated group developed postpartum endometritis. Berry 1994 also reported no cases of wound infection (Analysis 5.3) or required readmission to the hospital (Analysis 5.5).

Comparison 6. Different dosages/regimens of antibiotics

Primary outcomes

Not reported.

Secondary outcomes

One study (Mitra 1997) evaluated the effectiveness of once-daily versus thrice-daily gentamicin/clindamycin and found no differences in the rate of treatment failure (one trial, 131 women; RR 1.02, 95% CI 0.27 to 3.89; Analysis 6.1) and nephrotoxicity (no cases in any arm; Analysis 6.2) or in mean days of length of treatment (one trial, 131 women; MD -0.30, 95% CI -.90 to 0.30; Analysis 6.3).

Comparison 7. Antibiotics versus antibiotics

Primary outcomes

A significant difference favoring the short arm of treatment was found in one study (Edwards 2003) in mean duration of hospital stay (one trial, 292 women; MD -0.90, 95% CI -1.64 to -0.16; Analysis 7.1).

Secondary outcomes

Meta-analysis of two studies (Chapman 1997; Edwards 2003) revealed no significant differences in the rate of treatment failure when vaginal delivery was assessed (284 women; average RR 1.46, 95% CI 0.39 to 5.51; Tau^2 = 0.33; $I^{2=}$ 36%; Analysis 7.4). In addition, no significant differences were found in one study in rates of treatment failure with vaginal and cesarean delivery (one trial, 292 women; RR 1.31, 95% CI 0.42 to 4.02; Analysis 7.2), treatment failure with cesarean delivery (one trial, 117 women; RR 3.31, 95% CI 0.38 to 28.75; Analysis 7.3), wound infection (one trial, 292 women; RR 1.87, 95% CI 0.17 to 20.37; Analysis 7.5), and pelvic abscess (one trial, 292 women; RR 2.80, 95% CI 0.12 to 68.24; Analysis 7.6).

Intrapartum versus postpartum

Comparison 8. Antibiotics versus antibiotics

Primary outcomes

One study (Gibbs 1988) evaluated the use of ampicillin/gentamicin during intrapartum versus immediate postpartum and found significant differences favoring the intrapartum group in mean number of days of maternal postpartum hospital stay (one trial, 45 women; MD -1.00, 95% CI -1.94 to -0.06; Analysis 8.2) and mean number of neonatal hospital stay days (one trial, 45 neonates; MD -1.90, 95% CI -3.31 to -0.49; Analysis 8.7). Although no clear differences were found in rates of maternal bacteremia (one trial, 45 women; RR 2.19, 95% CI 0.25 to 19.48; Analysis 8.4) and early neonatal sepsis (one trial, 45 neonates; RR 0.08, 95% CI 0.00 to 1.44; Analysis 8.5), and a significant difference favoring intrapartum treatment was noted in relation to the outcome of neonatal pneumonia or sepsis (one trial, 45 neonates; RR 0.06, 95% CI 0.00 to 0.95; Analysis 8.6).

Secondary outcomes

One study (Gibbs 1988) evaluated the use of ampicillin/gentamicin during intrapartum versus immediate postpartum and found significant differences favoring the intrapartum group in mean maternal febrile days (Analysis 8.3).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Antibiotics versus no treatment during postpartum period for management of intra-amniotic infection

Population: women with management of intra-amniotic infection
Settings: 2 hospitals in USA
Intervention: antibiotics vs no treatment during postpartum period

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotics versus no treatment during postpartum period				
Neonatal death	Study population		RR 3.32 (0.14 to 79.88)	116 (1 study)	⊕◯◯◯ Very low[a,b]	
	Not estimable					
	Moderate					
	Not estimable					
Neonatal sepsis	Study population		RR 1.11 (0.23 to 5.27)	55 (1 study)	⊕◯◯◯ Very low[a,b]	
	148 per 1000	55 per 1000 (11 to 259)				
	Moderate					
	148 per 1000	54 per 1000 (11 to 258)				
Postpartum endometritis	Study population		RR 1.48 (0.68 to 3.24)	116 (1 study)	⊕◯◯◯ Very low[a,b]	

	148 per 1000	**218 per 1000** (100 to 478)				
	Moderate					
	148 per 1000	**219 per 1000** (101 to 480)				
Duration of maternal and neonatal hospital stay	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Need for additional antibiotic therapy	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Postpartum readmission for endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Failure of treatment	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] One study with design limitations.
[b] Wide confidence interval crossing the line of no effect, few events, and small sample size.

Antibiotics versus placebo during postpartum period for management of intra-amniotic infection

Population: women with management of intra-amniotic infection
Settings: hospitals in USA
Intervention: antibiotics vs placebo during postpartum period

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotics versus placebo during postpartum period				
Maternal and neonatal mortality	Study population		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Maternal and neonatal severe infection	Study population		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Duration of maternal and neonatal hospital stay	Study population		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					

Endomyometritis	See comment	See comment	Not estimable	288 (2 studies)	See comment	This outcome was reported with no events.
Need for additional antibiotic therapy	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Postpartum readmission for endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Treatment failure	**Study population**		**RR 0.97** (0.14 to 6.77)	288 (2 studies)	⊕◯◯◯ **Very low**[a,b]	The outcome was reported with no events in one study.
	14 per 1000	**14 per 1000** (2 to 97)				
	Moderate					
	8 per 1000	**8 per 1000** (1 to 54)				

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] One study with serious design limitations.
[b] Wide confidence interval crossing the line of no effect and small sample size.

Antibiotic versus antibiotics during postpartum period for management of intra-amniotic infection

Population: women with management of intra-amniotic infection
Settings: obstetric service in North Carolina
Intervention: antibiotic vs antibiotics during postpartum period

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic versus antibiotics during postpartum period				
Maternal and neonatal mortality	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Maternal and neonatal severe infection	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Length of treatment (days)		Mean length of treatment (days) in the intervention groups was **0.3 lower** (0.9 lower to 0.3 higher)		131 (1 study)	⊕◯◯◯ **Very low**[a,b]	Once daily versus thrice daily.

Endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Postpartum readmission for endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Treatment failure	**Study population**		**RR 1.02** (0.27 to 3.89)	131 (1 study)	⊕◯◯◯ **Very low**[a,b]	Once daily versus thrice daily.
	61 per 1000	**62 per 1000** (16 to 236)				
	Moderate					
	61 per 1000	**62 per 1000** (16 to 237)				

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] One study with design limitations.
[b] Wide confidence interval crossing the line of no effect and small sample size.

Antibiotics (short duration) compared with antibiotics (long duration) postpartum for management of intra-amniotic infection

Population: women with management of intra-amniotic infection
Settings: Delivery Unit at Shands Hospital at the University of Florida
Intervention: antibiotics (short duration)
Comparison: antibiotics (long duration) in postpartum

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antibiotics (long duration) postpartum	Antibiotics (short duration)				
Maternal and neonatal mortality	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Wound infection	**Study population**		**RR 1.87** (0.17 to 20.37)	292 (1 study)	⊕⊕◯◯ **Low**[a]	
	7 per 1000	**13 per 1000** (1 to 144)				
	Moderate					
	7 per 1000	**13 per 1000** (1 to 143)				
Duration of hospital stay (days)		Mean duration of hospital stay (days) in the intervention groups was **0.9 lower**		292 (1 study)	⊕⊕⊕◯ **Moderate**[b]	

		(1.64 to 0.16 lower)				
Need for additional antibiotic therapy	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Postpartum readmission for endometritis	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Treatment failure (vaginal and cesarean delivery)	**Study population**		**RR 1.31** (0.42 to 4.02)	292 (1 study)	⊕⊕◯◯ **Low**[a]	
	35 per 1000	**46 per 1000** (15 to 143)				
	Moderate					

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Wide confidence interval crossing the line of no effect and small sample size.
[b] Estimate based on small sample size.

Intrapartum compared with postpartum treatment

Population: women with management of intra-amniotic infection
Settings: a tertiary care facility
Intervention: intrapartum
Comparison: postpartum

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		Intrapartum				
Maternal and neonatal mortality	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					
Maternal bacteremia	**Study population**		**RR 2.19** (0.25 to 19.48)	45 (1 study)	⊕◯◯◯ **Very low**[a,b]	
	53 per 1000	**115 per 1000** (13 to 1000)				
	Moderate					
	53 per 1000	**116 per 1000** (13 to 1000)				
Early neonatal sepsis	**Study population**		**RR 0.08** (0 to 1.44)	45 (1 study)	⊕◯◯◯ **Very low**[a,b]	
	211 per 1000	**17 per 1000** (0 to 303)				

	Moderate					
	211 per 1000	**17 per 1000** (0 to 304)				
Neonatal pneumonia or sepsis	**Study population**		**RR 0.06** (0 to 0.95)	45 (1 study)	⊕○○○ **Very low**[a,c]	
	316 per 1000	**19 per 1000** (0 to 300)				
	Moderate					
	316 per 1000	**19 per 1000** (0 to 300)				
Maternal postpartum hospital stay (days)		Mean maternal postpartum hospital stay (days) in the intervention groups was **1 lower** (1.94 to 0.06 lower)		45 (1 study)	⊕○○○ **Very low**[a,b]	
Neonatal hospital stay		Mean neonatal hospital stay in the intervention groups was **1.9 lower** (3.31 to 0.49 lower)		45 (1 study)	⊕○○○ **Very low**[a,d]	
Endometritis/Failure treatment	**Study population**		Not estimable	0 (0)	See comment	This outcome was not reported in any of the included studies
	See comment	See comment				
	Moderate					

*The basis for the **assumed risk** (eg, median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] One study with serious design limitations.
[b] Wide confidence interval crossing the line of no effect and small sample size.
[c] Wide confidence interval.
[d] Small sample size.

DISCUSSION

Summary of main results

This review updates a previous Cochrane review (Hopkins 2002) with new references and expands the scope of the review to include antibiotic regimens during the postpartum period.

Although the review identified 11 eligible studies, information is insufficient to reveal the most appropriate antimicrobial regimen for the treatment of patients with intra-amniotic infection; whether antibiotics should be continued during the postpartum period; and which antibiotic regimen or what treatment duration should be used. Regarding maternal primary outcomes, four studies provided data on maternal hospital stay (Edwards 2003; Gibbs 1988; Lyell 2010; Mitra 1997) and two on severe infection (Berry 1994; Gibbs 1988); five provided data on neonatal severe infection (Gibbs 1988; Locksmith 2005; Lyell 2010; Maberry 1991; Turnquest 1998) and one on neonatal hospital stay (Gibbs 1988).

During labor

No significant differences were found between groups for any reported maternal or neonatal primary outcome when two different dosages/regimens of gentamicin were assessed. Meta-analysis of two studies found no significant differences in the rate of neonatal sepsis (low quality of evidence), treatment failure (endometritis) (low quality of evidence), or postpartum hemorrhage (low quality of evidence). The review did not identify data for a comparison of antibiotics versus no treatment/placebo.

Postpartum

No significant differences were found in rates of neonatal death and postpartum endometritis when use of antibiotics was compared with no treatment. Meta-analysis of two studies that evaluated the use of antibiotics versus placebo after vaginal delivery showed no significant differences between groups in rates of treatment failure or postpartum endometritis. Four trials assessing two different dosages/regimens of gentamicin or dual-agent therapy versus triple-agent therapy, or comparing antibiotics, did not find significant differences for most reported neonatal or maternal outcomes; however, the duration of hospital stay showed a difference in favor of the group of women who received short-duration antibiotics (moderate quality of evidence).

Intrapartum versus postpartum

Based on the findings of one small randomized controlled trial (RCT) (with data from 45 women), antepartum antibiotic treatment was found superior to postpartum antibiotic treatment in the mean number of days of maternal postpartum and neonatal hospital stay and in rates of neonatal pneumonia or sepsis. However, this study is at unclear risk of bias for all domains except random sequence generation, and the level of evidence was judged as very low for all outcomes. When studies conducted in the antepartum period were assessed, no evidence was found that use of a higher dose of antibiotics is superior to use of a lower dose in improving neonatal and maternal outcomes. With regards to the postpartum period, no evidence was found that using different types of antibiotics or longer or shorter treatment periods improves neonatal and maternal outcomes. It has to be noted that all women who participated in postpartum trials received antibiotics during the antepartum period.

Overall completeness and applicability of evidence

Although reasonable numbers of RCTs and participants were included in this review, the data are incomplete for several clinically important outcomes, and few data could be pooled in most comparisons. For example, data on primary prespecified outcomes (neonatal maternal and/or neonatal mortality; maternal and/or neonatal severe infection; and duration of maternal and/or neonatal hospital stay) were available in only a few studies.

Differences in the inclusion criteria and in outcomes definitions were noted, which made it difficult to interpret the results of the review and to determine their applicability. Outcome measures such as 'treatment failure' were clinically defined in different ways; follow-up times were heterogeneous; and adverse events were not frequently reported or were not even defined. Therefore, the results presented in this review are still limited.

Applicability of evidence outside the research setting is reasonable, as all of these studies were conducted in clinical settings that were quite similar. Comparisons described in the review are commonly undertaken and are not difficult to apply. Most trials were conducted in the United States of America, and no studies from low- or middle-income countries were included.

The following antibiotics were assessed in the included trials: ampicillin, ampicillin/sulbactam, gentamicin, clindamycin, and cefotetan. Antibiotic resistance is a growing phenomenon, and many factors may influence antibiotic use and resistance at the country level (Lamont 2014).

As a result of these limitations, it was not possible to generate definitive evidence on the effects of antibiotics in women with intra-amniotic infection.

Quality of the evidence

The quality of the evidence was low to very low for most outcomes, as per the GRADE approach. Only one outcome (duration of hospital stay) - comparison of antibiotics of short duration versus antibiotics of long duration postpartum for management of intra-amniotic infection-was considered to provide moderate quality of evidence. Main reasons to downgrade the quality of evidence were

limitations in study design or execution (risk of bias), Imprecision, and Inconsistency of results.

Risk of bias of the RCTs was mainly low or uncertain, and many studies had small sample sizes. Overall the studies had moderate risk of bias (see Figure 2; Figure 3), mainly because allocation concealment methods were not adequately reported and no blinding was performed. Methods used for sequence generation were adequately reported in most trials.

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

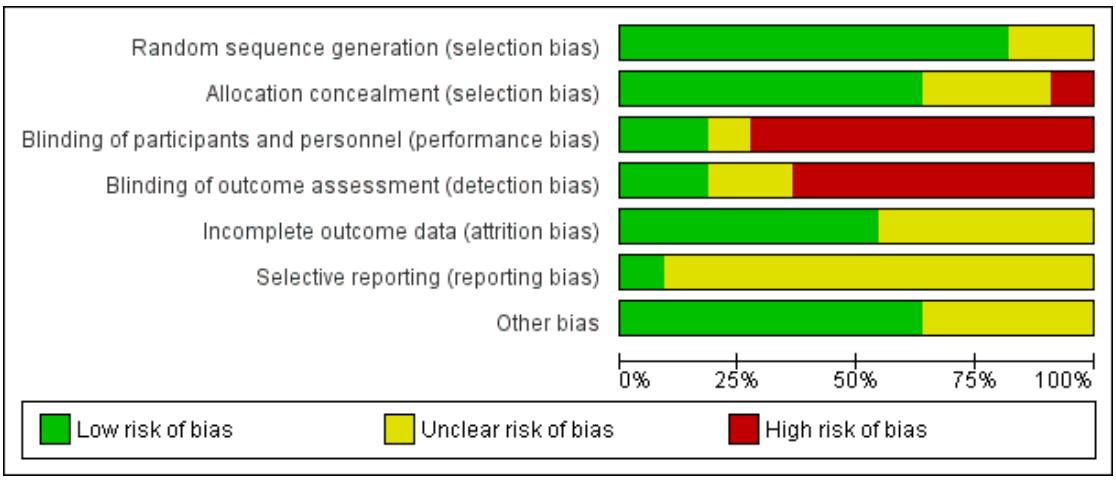
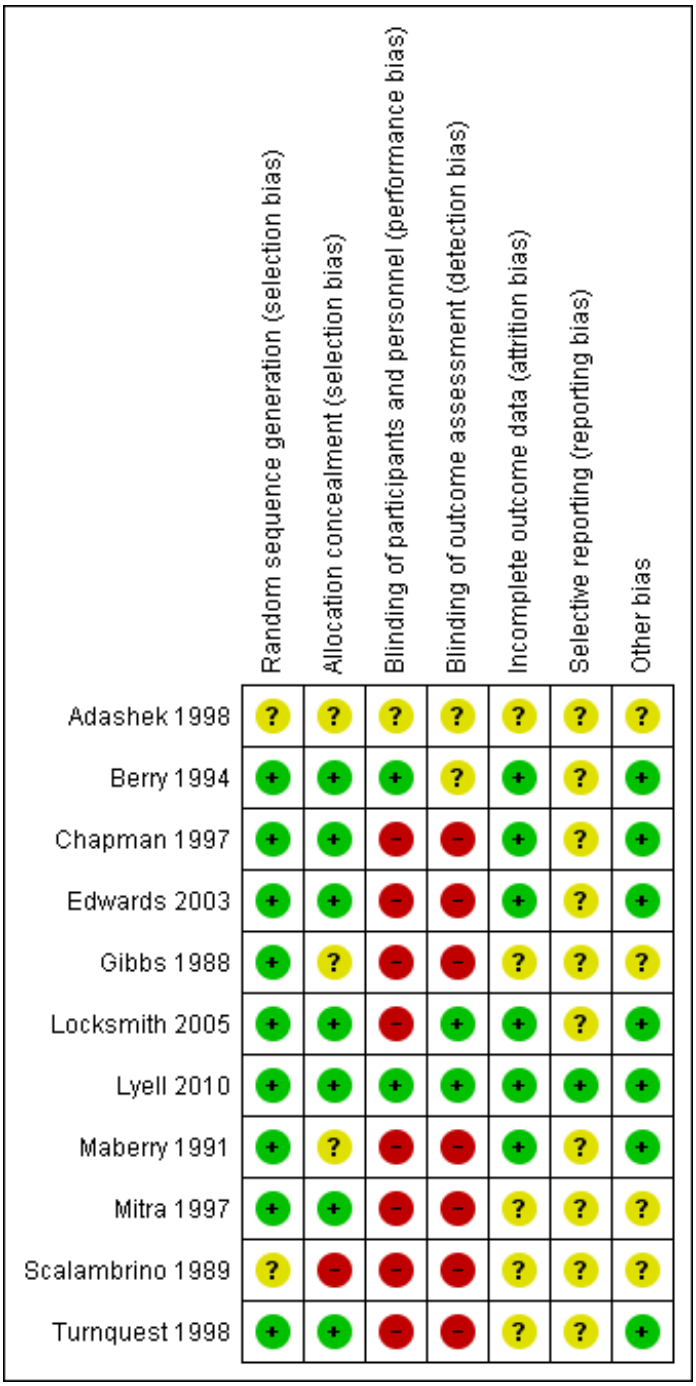


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Loss of participants in the included trials was generally low, although sample sizes were small for a number of them; in addition, most studies did not report how the sample size was calculated. Another limitation was incomplete outcome reporting (eg, continuous outcomes failed to provide standard deviations in several RCTs), and baseline characteristics were not reported, or statistically significant differences in baseline conditions were noted between treatment groups. Furthermore, none of the RCTs reported all prespecified primary outcomes of this review.

A high degree of heterogeneity was observed between studies in terms of interventions evaluated, concomitant treatments (other antibiotics), types of delivery, and outcomes assessed. Publication bias could not be evaluated, given the small number of trials identified for each comparison.

These factors make it difficult to determine the effectiveness of antibiotics in intra-amniotic infection and limit the assessment of risk of bias.

When comparing daily gentamicin versus eight hours of gentamicin, we graded treatment failure (endometritis), blood transfusion, maternal postpartum hospital stay, neonatal sepsis, and respiratory distress syndrome as "low quality of the evidence" because of the small sample size, and because the confidence interval overlaps 'no effect' (Summary of findings for the main comparison). We could not assess maternal death because the outcome was reported with no events. When comparing dual-agent therapy versus triple-agent therapy, we judged the quality of evidence on neonatal deaths as very low because one study had design limitations and wide confidence intervals crossing the line of no effect with small sample size.

When comparing antibiotics versus no treatment during the postpartum period, we graded postpartum endometritis, neonatal sepsis, and neonatal death as having very low quality of evidence caused by limitations of the study design and wide confidence intervals crossing the line of no effect with small sample sizes (Summary of findings 2). No included studies reported outcomes of duration of maternal and neonatal hospital stay, need for additional antibiotic therapy, postpartum readmission for endometritis, or failure of treatment.

When comparing antibiotics versus placebo during the postpartum period, we judged treatment failure as having "very low quality of the evidence" because of design limitations and wide confidence intervals crossing the line of no effect (Summary of findings 3). For the outcome of endomyometritis, two included studies reported no events. No included studies reported outcomes of maternal and neonatal mortality, maternal and neonatal severe infection, duration of maternal and neonatal hospital stay, need for additional antibiotic therapy, and postpartum readmission for endometritis.

When comparing once-daily versus thrice-daily antibiotics during the postpartum period, we judged treatment failure and duration of treatment as having very low quality of the evidence as the result of a single study with design limitations and wide confidence intervals crossing the line of no effect (Summary of findings 4). No included studies reported outcomes of maternal and neonatal mortality, maternal and neonatal severe infection, duration of maternal and neonatal hospital stay, endometritis, and postpartum readmission for endometritis.

When comparing short-duration antibiotics versus long-duration antibiotics given during the postpartum period, duration of hospital stay was significantly shorter in the short-duration group and the quality of the evidence was assessed as moderate. Treatment failure was graded as "low quality of the evidence" because of wide confidence intervals crossing the line of no effect (Summary of findings 5). No included studies reported outcomes of maternal and neonatal mortality, need for additional antibiotic therapy, endometritis, and postpartum readmission for endometritis.

When comparing intrapartum versus postpartum treatment, we judged maternal postpartum hospital stay, maternal bacteremia, early neonatal sepsis, neonatal pneumonia or sepsis, and neonatal hospital stay as having very low risk because a single study had serious design limitations and wide confidence intervals with a small sample size (Summary of findings 6). No included studies reported outcomes of endometritis, treatment failure, and maternal and neonatal mortality.

Potential biases in the review process

To minimize the risk of publication bias, we performed a comprehensive search of studies. We found that no RCTs were conducted in low- or middle-income countries, and all but one of the trials were conducted in the USA. Given the importance of the topic, it seems that we cannot rule out distortion of results by this type of bias.

Although some differences in interventions and outcomes were noted, a number of meta-analyses were performed. Small differences in dosage, regimen, or type of antibiotic could limit interpretation of pooled findings. Also, lack of information regarding main outcomes (eg, standard deviation around the mean in several trials) did not allow us to perform a pooled estimation in some trials. This may have hindered consideration of all relevant information available for each comparison.

Agreements and disagreements with other studies or reviews

Several systematic reviews have evaluated use of antibiotics during labor in other types of infection and in other conditions.

Kenyon 2013 found that using antibiotics for women with preterm rupture of the membranes significantly reduced rates of chorioamnionitis, neonatal infection, and other neonatal outcomes, while

increasing the risk of neonatal necrotizing enterocolitis (when co-amoxiclav was used); no significant reduction in perinatal mortality was found.

Ohlsson 2014 assessed the effects of intrapartum antibiotics for colonization of maternal group B hemolytic streptococci (GBS). The review authors found insufficient information from well-designed and well-conducted RCTs to support the use of antibiotics in reducing mortality from any cause.

Baaqeel 2013 evaluated the timing of administration of prophylactic antibiotics for cesarean section. Although the systematic review found that "compared with intraoperative administration, preoperative antibiotics significantly reduce the rate of endometritis," neonatal adverse effects must be assessed with a larger sample size. Also, Siriwachirachai 2010 evaluated the effectiveness of the use of prophylactic antibiotics for meconium aspiration syndrome during labor; they found that use of antibiotics could reduce the incidence of chorioamnionitis, but evidence was insufficient regarding other maternal and neonatal outcomes (eg, reduction in the incidence of neonatal sepsis). Evidence provided by the trials included in our review had similar limitations: Well-designed RCTs with adequate power are needed to identify statistically significant differences in main maternal and neonatal outcomes (mortality, severe infections), as well as in adverse events.

Tita 2010 reported that the typical regimen for treating clinical chorioamnionitis in labor is intravenous administration of ampicillin every six hours and gentamicin every eight to 24 hours until delivery. Clindamycin every eight hours (or metronidazole) is often added when cesarean delivery is performed.

One other study (Roberts 2012) reported that 96% of cases of histologic chorioamnionitis occurred without infection; study authors suggested that "infection is not the major cause of histologic chorioamnionitis among low-risk women at term," and therefore, intra-amniotic inflammation is not always due to infection. It has to be noted that study authors reported that histologic chorioamnionitis was strongly associated with fever (69% of febrile women) and was significantly related to epidurals used for pain relief. Future research is needed to determine the role of other factors (such as use of epidurals) in the appearance of fever, which is a key aspect of the intra-amniotic diagnosis. Intra-amniotic infection is frequently defined as "maternal fever in association with at least one additional clinical criterion including maternal or fetal tachycardia, maternal leukocytosis, uterine tenderness, or foul amniotic fluid odor" (Fishman 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Currently, no evidence has been found to show the most appropriate antimicrobial regimen for the treatment of patients with intra-amniotic infection; whether antibiotics should be continued during the postpartum period; and which antibiotic regimen or what treatment duration should be used. Also, evidence concerning the safety of antibiotic use is limited. One randomized controlled trial with small sample size showed that using antibiotics in the intrapartum period is superior using them in the postpartum period for reducing the number of days of maternal postpartum hospital stay, the days of maternal fever, and the number of neonatal hospital stay days (very low quality evidence), as well as the rate of neonatal pneumonia or sepsis (both very low quality of evidence).

Implications for research

Future randomized trials should be rigorously designed and conducted. The design and implementation of future studies should guarantee adequate concealment of the randomization sequence, as well as blinding of participants and evaluators of outcomes. Well-powered trials are needed to identify statistically significant differences among main maternal and neonatal outcomes (mortality, severe infections), as well as adverse events. Standardized definitions of the outcomes, the follow-up periods, and sources of information (phone, charts, appointment, etc) are also needed. Newer antibiotics/regimens such as pipericillin/tazobactam, quinolones, and cephalosporins, among others that may address developing resistance should be assessed.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Pregnancy and Childbirth Group for assistance provided.

We also would like to thank Erika Ota for developing the 'Summary of findings' table for this review. Erika Ota's work was financially supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization. The named review authors alone are responsible for the views expressed in this publication.

Ludovic Reveiz has contributed to this review mostly in a personal capacity and during spare time. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Organization. Evelina Chapman is a PhD candidate at the Universitat Autonoma de Barcelona.

Ludovic Reveiz is an employee of the Pan American Health Organization (PAHO) but has contributed to this Cochrane review during his own spare time, not as part of his role at PAHO.

As part of the prepublication editorial process, this review has been commented on by four peers (an editor and three referees, who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers, and the Group's statistical advisor.

REFERENCES

References to studies included in this review

Adashek 1998 *{published data only}*

Adashek JA, Asarat T, Lagrew DC, Rumney PJ, Adhoot D, Iriye BK, et al.The effect of antibiotics after a vaginal delivery complicated by chorioamnionitis in preventing the development of postpartum endomyometritis: a prospectively randomized double-blind placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1998; **178**(1 Pt 2):S212.

Berry 1994 *{published data only}*

* Berry C, Hansen KA, McCaul JF. Abbreviated antibiotic therapy for clinical chorioamnionitis: a randomized trial. *Journal of Maternal-Fetal Medicine* 1994;**3**(5):216–8.

Berry C, Hansen KA, McCaul JF. Single dose antibiotic therapy for clinical chorioamnionitis prior to vaginal delivery. *American Journal of Obstetrics and Gynecology* 1992;**166**:441.

Chapman 1997 *{published data only}*

Chapman S, Owen J. Randomized trial of single dose versus multiple dose cefotetan for the postpartum treatment of intrapartum chorioamnionitis. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S59.

* Chapman SJ, Owen J. Randomized trial of single-dose versus multiple-dose cefotetan for the postpartum treatment of intrapartum chorioamnionitis. *American Journal of Obstetrics and Gynecology* 1997;**177**(4):831–4.

Edwards 2003 *{published data only}*

Edwards RK, Duff P. One additional dose of antibiotics is sufficient postpartum therapy for chorioamnionitis [abstract]. *Infectious Diseases in Obstetrics and Gynecology* 2004;**12**(3/4):167.

* Edwards RK, Duff P. Single additional dose postpartum therapy for women with chorioamnionitis. *Obstetrics & Gynecology* 2003;**102**(5 Pt 1):957–61.

Gibbs 1988 *{published data only}*

Gibbs RS, Dinsmoor MJ, Newton ER, Ramamurthy RS. A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. *Obstetrics & Gynecology* 1988;**72**:823–8.

Locksmith 2005 *{published data only}*

Locksmith G, Chin A, Vu T, Shattuck K, Hankins G. High versus standard dosing of gentamicin in women with chorioamnionitis: a randomized, controlled, pharmacokinetic analysis [abstract]. *American Journal of Obstetrics and Gynecology* 2003;**189**(6 Suppl 1):S103.

* Locksmith GJ, Chin A, Vu T, Shattuck KE, Hankins GDV. High compared with standard gentamicin dosing for chorioamnionitis: a comparison of maternal and fetal serum drug levels. *Obstetrics & Gynecology* 2005;**105**:473–9.

Lyell 2010 *{published data only}*

* Lyell DJ, Pullen K, Fuh K, Zamah AM, Caughey AB, Benitz W, et al.Daily compared with 8-hour gentamicin for the treatment of intrapartum chorioamnionitis: a randomized controlled trial. *Obstetrics & Gynecology* 2010; **115**(2 Pt 1):344–9.

Pullen K, Zamah M, Fuh K, Caughey A, Benitz W, Lyell D, et al.Once daily vs. 8 hour gentamicin dosing for chorioamnionitis. *American Journal of Obstetrics and Gynecology* 2007;**197**(6 Suppl 1):S68.

Maberry 1991 *{published data only}*

Maberry M, Gilstrap L, Burris J, Bawdon R, Leveno K. A randomized comparative study of triple antibiotic therapy in the management of acute chorioamnionitis. Proceedings of 9th Annual Meeting of the Society of Perinatal Obstetricians; 1989 Feb 1-4; New Orleans, Louisiana, USA. 1989:465.

* Maberry MC, Gilstrap LC, Bawdon R, Little BB, Dax J. Anaerobic coverage for intra-amnionic infection: maternal and perinatal impact. *American Journal of Perinatology* 1991;**8**:338–41.

Mitra 1997 *{published data only}*

Mitra AG, Whitten K, Laurent SL, Anderson WE. A randomized, prospective study comparing once-daily gentamicin versus thrice-daily gentamicin in the treatment of puerperal infection. *American Journal of Obstetrics and Gynecology* 1997;**177**(4):786–92.

Scalambrino 1989 *{published data only}*

Scalambrino S, Mangioni C, Milani R, Regallo M, Norchi S, Negri L, et al.Sulbactam/ampicillin vs cefotetan in the treatment of obstetric and gynecologic infections. *International Journal of Gynecology & Obstetrics* 1989;**Suppl 2**:21–7.

Turnquest 1998 *{published data only}*

Turnquest MA, How HY, Cook CR, O'Rourke TP, Cureton AC, Spinnato JA, et al.Chorioamnionitis: is continuation of antibiotic therapy necessary after cesarean section?. *American Journal of Obstetrics and Gynecology* 1998;**179**(5): 1261–6.

References to studies excluded from this review

Budanov 2000 *{published data only}*

Budanov PV, Baev OR, Musaev ZM. Features of antibacterial therapy intraamniotic infections [abstract]. *XVI FIGO World Congress of Obstetrics & Gynecology; 2000 Sept 3-8; Washington DC, USA* 2000;**Book 1**:66.

Creatsas 1980 *{published data only}*

Creatsas G, Pavlatos M, Lolis D, Kaskarelis D. Ampicillin and gentamicin in the treatment of fetal intrauterine infections. *Journal of Perinatal Medicine* 1980;**8**:13–8.

La-Bella 1996 *{published data only}*

La-Bella C, Sandberg P, Edelstone D. Labor-related intra-amniotic infection-is postpartum treatment necessary when delivery occurs vaginally?. *American Journal of Obstetrics and Gynecology* 1996;**174**(1 Pt 2):404.

McCredie 1956 *{published data only}*

McCredie Smith JA, Jennison RF, Langley FA. Perinatal infection and perinatal death: clinical aspects. *Lancet* 1956; **2**:903–6.

Rocha 1999 *{published data only}*

Rocha JE, Duarte G, Cunha S, Nogueira AA, Mauad F. Ampicillin prophylaxis in premature rupture of membranes: randomized and double-blind study [Antibioticoprofilaxia com ampicilina na rotura prematura das membranas: estudo randomizado e duplo cego]. *Revista Brasileira de Ginecologia e Obstetricia* 1999;**21**(5):251–8.

References to ongoing studies

Aziz 2009 *{published data only}*

Aziz N. Comparison of ampicillin/sulbactam vs. ampicillin/gentamicin for treatment of intrapartum chorioamnionitis: a randomized controlled trial. ClinicalTrials.gov (https://clinicaltrials.gov/) [accessed 21 May 2013] 2009.

Shanks 2012 *{published data only}*

Shanks A. Treatment utility of postpartum antibiotics in chorioamnionitis (TUPAC). ClinicalTrials.gov (https://clinicaltrials.gov/) (accessed September 2014). 2012.

Additional references

Baaqeel 2013

Baaqeel H, Baaqeel R. Timing of administration of prophylactic antibiotics for caesarean section: a systematic review and meta-analysis. *BJOG: an international journal of obstetrics and gynaecology* 2013;**120**(6):661–9.

Czikk 2011

Czikk MJ, McCarthy FP, Murphy KE. Chorioamnionitis: from pathogenesis to treatment. *Clinical Microbiology and Infection* 2011;**17**(9):1304–11.

Edwards 2005

Edwards R. Chorioamnionitis and labor. *Obstetrics and Gynecology Clinics of North America* 2005;**32**:287–96.

Fahey 2008

Fahey J. Clinical management of intra-amniotic infection and chorioamnionitis: a review of literature. *Journal of Midwifery & Women's Health* 2008;**53**(3):227–35.

Fishman 2012

Fishman S, Gelber S. Evidence for the clinical management of chorioamnionitis. *Seminars in Fetal and Neonatal Medicine* 2012;**17**:46–50.

Getahun 2010

Getahun D, Strickland D, Zeiger RS, Fassett MJ, Chen W, Rhoads GG, et al.Effect of chorioamnionitis on early childhood asthma. *Archives of Pediatrics and Adolescent Medicine* 2010;**164**(2):187–92.

Gibbs 2004

Gibbs R. Management of clinical chorioamnionitis at term. *American Journal of Obstetrics and Gynecology* 2004;**191**: 1–2.

GRADE 2008

Brozek J, Oxman A, Schünemann H. GRADEpro. 3.6. The Cochrane Collaboration, 2008.

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Holzman 2007

Holzman C, Lin X, Senagore P, Chung H. Histologic chorioamnionitis and preterm delivery. *American Journal of Epidemiology* 2007;**166**(7):786–94.

Incerpi 2010

Incerpi MH. Chorio-amnionitis and postpartum endometritis. In: Goodwin TM, Montoro MN, Muderspach L, Paulson R, Roy S editor(s). *Management of Common Problems in Obstetrics and Gynecology*. Oxford: Blackwell Publishing Ltd, 2010.

Kenyon 2013

Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. *Cochrane Database of Systematic Reviews* 2013, Issue 12. [DOI: 10.1002/14651858.CD001058.pub3]

Lamont 2014

Lamont HF, Blogg HJ, Lamont RF. Safety of antimicrobial treatment during pregnancy: a current review of resistance, immunomodulation and teratogenicity. Expert Opinion on Drug Safety 2014 Sept 5 [Epub ahead of print]:1–13. [PUBMED: 25189188]

López-Zeno 1992

López-Zeno JA, Peaceman AM, Adashek JA, Socol ML. A controlled trial of a program for the active management of labor. *New England Journal of Medicine* 1992;**326**:450–4.

Manríquez 2008

Manríquez JJ. A highly sensitive search strategy for clinical trials in Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS) was developed. *Journal of Clinical Epidemiology* 2008;**61**(4):407–11.

Mozurkewich 1997

Mozurkeqich E, Wolf F. Premature rupture of membranes at term: a meta-analyses of three management schemes. *Obstetrics and Gynecology* 1997;**89**:1035–43.

Mtira 1997
Mitra A, Whitten K, Laurent S, Anderson W. A randomized, prospective study comparing once-daily gentamicin versus thrice-daily gentamicin in the treatment of puerperal infection. *American Journal of Obstetrics and Gynecology* 1997;**177**(4):786–92.

Newton 1989
Newton E, Prihoda T, Gibbs R. Logistic regression analysis of risk factors for intra-amniotic infection. *Obstetrics and Gynecology* 1989;**73**(4):571–5.

Ohlsson 2014
Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD007467.pub4]

RevMan 2014
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2012
Roberts DJ, Celi AC, Riley LE, Onderdonk AB, Boyd TK, Johnson LC, et al.Acute histologic chorioamnionitis at term: nearly always noninfectious. *Plos One* 2012;**7**(3):e31819.

Rocha 2007
Rocha G, Proenca E, Wuintas C, Rodrigues T, Guimaraes H. Chorioanmionitis and brain damage in the preterm newborn. *Journal of Maternal-Fetal and Neonatal Medicine* 2007;**20**(10):745–9.

Schunemann 2009
Schunemann HJ. GRADE: from grading the evidence to developing recommendations. A description of the system and a proposal regarding the transferability of the results of clinical research to clinical practice [GRADE: Von der Evidenz zur Empfehlung. Beschreibung des Systems und Losungsbeitrag zur Ubertragbarkeit von Studienergebnissen]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen* 2009;**103**(6):391–400. [PUBMED: 19839216]

Seaward 2005
Seaward G, Hannah M, Myhr T, Farine D, Ohlsson A, Wang E, et al.International multicentre term prelabor rupture of membranes study: evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabor rupture of membranes at term. *American Journal of Obstetrics and Gynecology* 2005;**177**(5):1024–9.

Siriwachirachai 2010
Siriwachirachai T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M. Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD007772.pub2]

Tita 2010
Tita A, Andrews W. Diagnosis and management of clinical chorioamnionitis. *Clinical Perinatology* 2010;**37**(2):339–54.

Wu 2000
Wu Y, Colfrod J. Chorioamnionitis as a risk factor for cerebral palsy. *JAMA* 2000;**284**(11):1417–24.

Yoon 2001
Yoon B, Romero R, Moon J, Shim S, Kim M, Kim G, et al.Clinical significance of intra-amniotic inflammation in patients with preterm labor and intact membranes. *American Journal of Obstetrics and Gynecology* 2001;**185**(5): 1130–6.

References to other published versions of this review

Chapman 2014
Chapman E, Reveiz L, Bonfill Cosp X. Antibiotic regimens for management of intra-amniotic infection. *Cochrane Database of Systematic Reviews* 2014, Issue 4. [DOI: 10.1002/14651858.CD010976]

Hopkins 2002
Hopkins L, Smaill F. Antibiotic regimens for management of intraamniotic infection. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003254]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adashek 1998

Methods	Randomized double-blind placebo-controlled trial. Conducted in the USA.
Participants	Women after vaginal delivery that was complicated by fever of ≤ 38.0°C Exclusion criteria: maternal fever ≥ 40°C, maternal sepsis, or use of steroids N = 250.
Interventions	Gentamicin and clindamycin (doses, regimen not stated) (n = 127) vs placebo (n = 123)
Outcomes	Treatment failure defined as persistent fever after the third dose of the study drug, or patient readmitted with postpartum endomyometritis
Notes	Full text not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of the method used for blinding interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of the method used for blinding interventions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description of losses.
Selective reporting (reporting bias)	Unclear risk	Insuficient information to permit judgment. Most relevant outcomes not reported
Other bias	Unclear risk	Baseline characteristics not reported.

Berry 1994

Methods	Randomized controlled trial.
Participants	**Inclusion criteria:** women with chorioamnionitis defined as oral temperature 38°C or higher and membranes ruptured **Exclusion criteria:** gestational age < 36 weeks; signs of intra-amniotic infection on admission; evidence of urinary, gastrointestinal, or pulmonary infection; maternal immune compromise; antibiotic therapy within 24 hours of admission; or, if delivery was > 6 hours, after initial dose of antibiotics; intra-amniotic infection on admission and participants who were not delivered in < 6 hours after initial dose of antibiotics **Setting:** Naval Hospital, Portsmouth, USA. Study period: July 1990 to May 1991 N = 41. 38 participants completed the protocol.
Interventions	At the time of diagnosis, women were treated with IV ampicillin 2.0 g and gentamicin 2.0 mg/kg. Following vaginal delivery, **treatment group** received IV ampicillin 2.0 g every 6 hours for 8 doses and gentamicin 2.0 mg/kg every 8 hours for 6 doses (n = 21) . Women in the **placebo group** received normal saline on an identical dosing schedule (n = 17)
Outcomes	Treatment failure: defined as temperature greater than 38°C after the first postpartum antibiotic or placebo dose, wound infection, sepsis, or required readmission to the hospital Women were given 6 weeks' postpartum clinic appointments and strict discharge instructions to return
Notes	Low-risk population. Intra-amniotic infection was diagnosed in 97 (4.3%) participants during their labor, and 63 (65%) had **vaginal deliveries.** 41 were initially enrolled in this study, 38 of whom completed the protocol with data available for interpretation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The pharmacy used a random number table to assign participants to treatment or placebo study group
Allocation concealment (selection bias)	Low risk	The pharmacy labeled placebo and antibiotic containers alike
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and healthcare providers were unaware of participants' treatment or placebo status
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant left the hospital against medical advice, and 2 were inadvertently discharged within 48 hours of observation. Therefore these 3 women were excluded from

Berry 1994 (*Continued*)

		analysis. "No patients develop treatment failure…. including the three patients who were excluded from analysis due their leaving the hospital prior to completing the protocol"
Selective reporting (reporting bias)	Unclear risk	Insuficient information to permit judgment. Main relevant outcomes not reported
Other bias	Low risk	No others biases noted.

Chapman 1997

Methods	Randomized controlled trial. Study period: January 1995 to November 1996.
Participants	**Inclusion criteria:** 1. Clinical diagnosis of intrapartum amnionitis: fever ≥ 38°C, and at least 1 of the following: maternal tachycardia (> 100 beats/min); fetal tachycardia (> 160 beats/min); maternal leukocytosis (> 15.000); uterine tenderness; or foul-smelling amniotic fluid. 2. Intrapartum treatment with ampicillin and gentamicin. 3. Vaginal delivery. **Exclusion criteria:** evidence of septic shock, another source of infection, or a penicillin allergy. **Setting:** university tertiary hospital and county hospital. Conducted in the USA Number of participants: 109 women; 55 in the short arm and 54 in the longer arm Study period: January 1995 to November 1996. N = 109.
Interventions	All women were treated with ampicillin and gentamicin during labor. Experimental group (n = 55): 1 single dose of cefotetan 2 g IV within 1 hour after delivery. Control group (n = 54): cefotetan 2 g IV every 12 hours for a minimum of 48 hours. Initial dose within 1 hour after delivery
Outcomes	Primary outcome: length of postpartum hospital stay. Secondary outcomes: 1. Duration of maternal febrile morbidity. 2. Failed treatment. 3. Need for alternate antibiotic therapy. After discharge, a research nurse called each participant within the first week to determine whether the women had additional symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Chapman 1997 (*Continued*)

Random sequence generation (selection bias)	Low risk	Random sequence generated by computer program.
Allocation concealment (selection bias)	Low risk	Use of consecutively numbered, sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was performed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding was performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses of follow-up until discharge. Follow-up at 7 days: 7 women could not be reached by phone: 4 in the experimental group, 3 in the control group
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgment. Not all relevant outcomes were reported, SDs were not reported
Other bias	Low risk	Baseline characteristics were similar among groups.

Edwards 2003

Methods	Randomized controlled trial.
Participants	Inclusion criteria: women with clinical chorioamnionitis and a plan of treatment with IV antibiotics and delivery. Clinical chorioamnionitis was "by a temperature of 38.0°C or more and 1 or more of the following findings: maternal heart rate 100 beats per minute, baseline fetal heart rate 160 beats per minute, uterine tenderness, or foul-smelling amniotic fluid" Exclusion criteria: women allergic to B-lactam antibiotics, immunocompromised, at risk for bacterial endocarditis, had received B-mimetic drugs in the preceding 8 hours, or had a concurrent febrile illness (eg, pyelonephritis) Setting: Delivery Unit at Shands Hospital at the University of Florida. Conducted in the USA Period of the study: December 1999 to March 2003. Number of participants: n = 292.
Interventions	When women were diagnosed with chorioamnionitis, they received IV ampicillin, 2 g every 6 hours, and gentamicin, 1.5 mg/kg every 8 hours "After delivery, women randomized to the control group (long arm; n=141) continued to receive ampicillin and gentamicin according to the above schedule until they were afebrile and asymptomatic for 24 hours;

	Women randomized to the study group (short arm; n=151) received only the next scheduled dose of each drug." Women in the study group who were delivered via cesarean received only the initial dose of clindamycin, 900 mg IV, and the control group received clindamycin every 8 hours until afebrile and asymptomatic for 24 hours
Outcomes	Main: treatment failure defined as body temperature reading after first postpartum dose of antibiotics, either once above 39.0°C or twice above 38.4°C, at least 4 hours apart Secondary outcomes: number of doses of antibiotics, duration of hospital stay, and infection-related complications
Notes	All women received this regimen of antibiotics until delivery: IV ampicillin, 2 g every 6 hours, and gentamicin, 1.5 mg/kg every 8 hours Participants identified as treatment failures immediately received IV ampicillin, 2 g every 6 hours, gentamicin, 7 mg/kg ideal body weight every 24 hours, and metronidazole, 500 mg every 12 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number-generating software program (Research Randomizer; Social Psychology Network, Middleton, CT) was used to assign participants to groups
Allocation concealment (selection bias)	Low risk	Using sequentially numbered sealed and opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not performed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 women (6.2%) experienced protocol violations, 5 (3, 5%) in the long arm and 13 in the short arm (8,6%). A per-protocol analysis was performed that excluded data from these 18 women. In this analysis, treatment failure rates were similar for the long arm (n = 136) and short arm (n = 138), respectively (2.9% vs 4.3%; P = 0.749) "Analysis of outcome variables was performed by intent to treat. We also performed a per-protocol analysis, excluding subjects who were enrolled in the study despite not having met all of the enrollment criteria or whose antibiotic therapy deviated from that prescribed by randomization."

Edwards 2003 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insuficient information to permit judgment. Not all expected outcomes were reported
Other bias	Low risk	No other biases were noted.

Gibbs 1988

Methods	Randomized controlled trial of intrapartum vs immediate postpartum antibiotic treatment of women with intra-amniotic infection
Participants	**Inclusion criteria:** women with clinical diagnosis of intrapartum amnionitis defined as maternal fever (37.8°C or higher) and rupture of the membranes, plus 2 or more of the following: maternal tachycardia, (more than 100 beats per minute), uterine tenderness, purulent or foul amniotic fluid, fetal tachycardia (more than 160 beats per minute), or maternal leukocytosis **Exclusion criteria:** gestational age below 34 weeks or cervical dilatation less than 4 cm at the time of diagnosis. **Setting:** a tertiary care facility. Conducted in the USA. **Number of participants:** 48 participants were enrolled in the trial: 26 assigned to intrapartum treatment, and 22 assigned to postpartum treatment
Interventions	Both groups received the same antibiotics, namely, ampicillin 2 g IV every 6 hours, plus gentamicin 1.5 mg/kg IV every 8 hours. Women delivered by cesarean section also received clindamycin 900 mg IV every 8 hours, beginning after cord clamping. Women were treated with IV antibiotics until they were afebrile for approximately 48 hours
Outcomes	Main outcome: neonatal sepsis defined as bacteremia or death with a clinical diagnosis of sepsis and positive cultures Secondary outcomes: other infections such as pneumonia, 5-minute Apgar $\leq$ 6, length of neonatal hospital stay 4 weeks after discharge, the mother was contacted by telephone or letter, and then hospital records were assessed for readmission
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Chosen by flipping a coin.
Allocation concealment (selection bias)	Unclear risk	Sealed envelope. No further description is provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not performed.

Gibbs 1988 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 22 assigned to postpartum treatment, 3 with protocol violations were excluded
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgment. Not all relevant outcomes were reported
Other bias	Unclear risk	Intrapartum group was significantly older than postpartum group (P = 0.03), but the clinical significance of this is doubtful, especially because nearly equal percentages were nulliparous

Locksmith 2005

Methods	Randomized controlled trial.
Participants	38 laboring women, at least 34 weeks' gestation, with clinical chorioamnionitis; "the diagnosis of chorioamnionitis was based on a fever during labor of at least 37.8°C combined with at least 1 of the following clinical signs: maternal heart rate greater than 100 beats per minute, fetal heart rate greater than 160 beats per minute, uterine tenderness, or malodorous amniotic fluid Exclusion criteria: women with a history of renal insufficiency or myasthenia gravis, serum creatinine level greater than 1.4 mg/dL, allergy to gentamicin, receipt of magnesium sulfate or a neuromuscular blocking agent within 24 hours of enrollment, hypocalcemia, or receipt of a diuretic agent within the week before enrollment Conducted in the USA.
Interventions	Participants were assigned to 1 of 2 gentamicin-dosing groups: 5.1 mg/kg every 24 hours (once daily; n = 18), or 120 mg followed by 80 mg every 8 hours (standard; n = 20) Ampicillin 2 g IV every 6 hours was provided to all participants
Outcomes	Duration of labor after a diagnosis of chorioamnionitis, cesarean delivery rate, length of febrile illness in the postpartum period, and length of hospitalization. Evaluations of specific maternal morbidity included puerperal infection, peripartum hemorrhage, need for blood transfusion, and death Neonatal outcomes of interest included Apgar scores, urine output (assessed by daily diaper counts), serum creatinine levels, suspected and confirmed sepsis rates, need for antibiotic therapy, length of antibiotic therapy, length of hospitalization, and death
Notes	

Risk of bias

Locksmith 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization schedule was created by using a computer-generated random number table
Allocation concealment (selection bias)	Low risk	Randomization was accomplished with sequentially numbered sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not performed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Review authors who assessed outcomes were blinded to assignment of participants to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses were reported.
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgment. Most relevant outcomes were reported
Other bias	Low risk	1 participant in the conventional dosing group received 2 gentamicin doses before delivery; the remainder received only 1 dose

Lyell 2010

Methods	Randomized double-blind controlled trial.
Participants	**Inclusion criteria:** women with chorioamnionitis defined as maternal temperature ≥ 38°C, without other sources of fever; with fetal tachycardia (> 160 beats) and/or maternal tachycardia (≥ 110 beats per minute); gestational age between 34 and 42 weeks. Maternal age 18 years or older. **Exclusion criteria:** allergy to ampicillin, gentamicin, or clindamycin. Preterm PROM. Chronic or transient renal disease, hearing loss, HIV; intrauterine fetal death, severe fetal anomalies. **Setting:** Labor and Delivery Unit at Lucile Packard Children's Hospital at Stanford University Medical Center. Conducted in the USA **Period of the study:** June 2004 to October 2006. N = 126.
Interventions	**Experimental group (n = 63):** ampicillin 2 g IV every 6 hours; gentamicin single dose 5 mg/kg, followed by saline placebo after 8 and 16 hours (every 8 hours). Clindamycin 900 mg. every 8 hours in case of cesarean delivery **Control group (n = 63):** ampicillin 2 g IV every 6 hours IV; gentamicin loading dose 2 mg/kg, followed by 1.5 mg/kg after 8 and 16 hours IV (every 8 hours). Clindamycine 900 mg every 8 hours IV in case of cesarean delivery

	Women who underwent cesarean delivery also received clindamycin (900 mg IV every 8 hours, for a total of 3 doses)
Outcomes	Primary outcome was treatment success, defined by resolution of chorioamnionitis after 16 hours of treatment without development of endometritis Primary outcome: 1. Resolution of fever (less than 38°C) by 16 hours after initiation of medications. 2. Without development, endometritis diagnosed based on fever greater than 38°C with uterine tenderness more than 24 hours after delivery. "All patients with an initial successful response to antibiotics in the hospital were called after 10 days after discharge to determine whether they had later developed endometritis based on a brief screening interview regarding development of fever or uterine tenderness. The primary outcome was determined based on chart review and follow-up phone calls by a single provider blinded to group allocation. All newborns were admitted to the Special Care Nursery for a sepsis evaluation."
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The pharmacist used a random number table.
Allocation concealment (selection bias)	Low risk	"The pharmacist assigned randomization from a random numbers table, prepared and dispensed all study drugs, and maintained blinding by sending identical-appearing medications labeled only with the patient's study number. Everyone except for the pharmacist remained blinded throughout the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing medications labeled only with the participant's study number
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical-appearing medications labeled only with the participant's study number
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman allocated to daily gentamicin was excluded from analysis because participant age was younger than 18 years
Selective reporting (reporting bias)	Low risk	Most relevant outcomes were reported, and the study was registered at clinicaltrials.gov

Other bias	Low risk	Baseline characteristics were reported and study was judged as having no risk of bias

Maberry 1991

Methods	Randomized controlled trial.
Participants	**Inclusion criteria:** women with diagnosis of intra-amniotic infection and gestational age greater than 24 weeks were included. Diagnosis of intra-amniotic infection was made on the basis of a temperature of 38°C or higher in the presence of labor and ruptured membranes. In addition, 1 or more of the following were present: maternal tachycardia, fetal tachycardia, uterine tenderness, or foul-smelling amniotic fluid **Exclusion criteria:** other sources of fever excluded before the diagnosis was made **Setting:** tertiary county hospital. Conducted in the USA. Period of the study: December 1987 to January 1991. N = 133.
Interventions	Ampicillin and gentamicin (dual therapy; n = 69) or ampicillin, gentamicin, and clindamycin (triple-agent therapy; n = 64)
Outcomes	Postpartum complications, endometritis, wound infection, need for additional antibiotics, length of hospital stay Diagnosis of endometritis was based on the presence of a temperature of 38°C or higher on at least 2 occasions, excluding the first postpartum day, or by persistence of a temperature of 38°C or higher 48 hours post delivery Newborn medical records were reviewed for assessing neonatal sepsis, pneumonia, respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Neonatal sepsis was defined as a positive blood or spinal fluid culture or a positive urine latex test for group B streptococcus
Notes	No details were provided about antibiotic doses and administration "The majority of infants born to mothers with intra-amniotic infection who were treated with antibiotic intrapartum received ampicillin and gentamicin for at least 48 hours pending blood culture results."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not performed.

Maberry 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Nor performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses were reported.
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgment.
Other bias	Low risk	No other biases were noted.

Mitra 1997

Methods	Randomized controlled trial.
Participants	**Inclusion criteria:** (1) 2 temperatures ≥ 100.4°F 6 hours apart, excluding the first 12 postpartum hours, (2) a single temperature ≥ 202°F in first 12 postpartum hours, (3) a diagnosis of chorioamnionitis in labor thought to require postpartum prophylactic antibiotic therapy, or (4) a diagnosis of postpartum participants with puerperal endometritis or with chorioamnionitis in labor assessed to be at risk for endometritis. Endometritis after initial discharge from the hospital **Exclusion criteria:** baseline serum creatinine level > 1.5 mg/dL, extrapelvic sources of infection, and allergy or hypersensitivity to either study drug. Before enrolment each woman underwent a history and physical examination as well as a laboratory evaluation comprising a complete blood cell count with differential, a urinalysis with culture, and a baseline serum creatinine concentration **Setting:** obstetric service in North Carolina. Conducted in the USA. Study period: July 1, 1994, through July 31, 1996. N = 272.
Interventions	Gentamicin 4 mg/kg IV every 24 hours with clindamycin 1200 mg IV every 12 hours (experimental arm) (n = 135) or gentamicin 1.33 mg/kg IV and clindamycin 800 mg IV every 8 hours (conventional dosing interval arm) (n = 137)
Outcomes	Cure rates, mean length of treatment, antibiotic-related charges, relapse, and nephrotoxicity "Cures were defined as an average temperature of <=99°F for 24 hours and the resolution of symptoms. Failure was defined as a persistently elevated temperature 72 hours after the initiation of antibiotic therapy, clinical deterioration, or the need for additional antibiotic or heparin therapy." "Relapse was defined as a cure with subsequent wound infection, abscess, or recurrent endometritis up to 6 weeks after delivery. Time to resolution of infection was calculated from time of the first dose to time that the last dose of antibiotic was administered. Cost of the treatment was obtained from pharmacy charges to participants, which included both the cost of medication and IV administrative charges
Notes	Participants were analyzed according to treatment assignment, reason for enrollment (chorioamnionitis vs endometritis), and route of delivery

Mitra 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated set of random numbers.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes opened in consecutive order.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Physicians were not blinded with respect to the dosing regimen
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Chorioamnionitis group: 12 of 17 (71%) women in the experimental arm versus 10 of 11 (91%) women in the conventional arm who were enrolled for an isolated temperature spike to 102°F in the first 12 postpartum hours had a vaginal delivery (P = 0.35). Study authors reported that even if these 2 groups of participants are excluded from analysis, the study still has power of 75% to detect a 15% difference in efficacy of the 2 treatment regimens
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgment. Protocol not available. Not all relevant outcomes were included
Other bias	Unclear risk	90 of 137 women (65.7%) in the conventional arm were delivered by cesarean section, whereas 71 of 135 (52.6%) women in the experimental arm had a cesarean delivery (P = 0.03). In a multiple logistic regression model, the 2 primary confounders for the outcome of cure were mode of delivery and reason for treatment (chorioamnionitis or endometritis). When reason for treatment (chorioamnionitis or endometritis) in the treatment regimen were controlled for, the relative risk for treatment failure was 4.7 (P = 0.02) for women delivered by cesarean section compared with women delivered vaginally

Scalambrino 1989

Methods	Open randomized clinical trial.
Participants	**Inclusion criteria:** women with chorioamnionitis defined by body temperature ≥ 38°in a single measurement before delivery. Other women with febrile disorder after delivery, complication of gynecologic surgery, non-surgical gynecologic infections, pelvic peritonitis, and tumors were also included **Exclusion criteria:** allergy to penicillin and or cephalosporin, participants with renal or hepatic function impairment. Women who had received antibiotic treatment the last week preceding the study. **Setting:** University hospital at Monza, Italy. Study period: January to December 1987.
Interventions	**Experimental group (n = 11):** ampicillin 1 g plus sulbactam 1 g IV every 8 hours at least for 96 hours (4 days), or until 24 hours after disappearance of all symptoms of infection. **Control group (n = 8):** cefotetan 2 g every 12 hours at least for 96 hours (4 days), or until 24 hours after disappearance of all symptoms of infection
Outcomes	Failure (ineffective treatment). Treatment was considered ineffective when signs and symptoms and/or temperature curve remained unchanged or rose during the first 72 hours of treatment Microbiological cultures; adverse effects were considered.
Notes	We considered only women with chorioamnionitis (19/95 participants). Outcomes other than failure of antibiotic treatment for women with chorioamnionitis were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No report.
Allocation concealment (selection bias)	High risk	No report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly stated for the chorioamnionitis subgroup.
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgment. Not all relevant outcomes were reported

Scalambrino 1989 (*Continued*)

Other bias	Unclear risk	Information was insufficient to permit judgment.

Turnquest 1998

Methods	Randomized controlled trial.
Participants	**Inclusion criteria:** women with a clinical diagnosis of chorioamnionitis treated with ampicillin during labor and who required cesarean delivery for obstetric indications. "A diagnosis of clinical chorioamnionitis was made if maternal oral temperature was ≥100. 4°F with any of the following conditions: malodorous amniotic fluid, uterine tenderness, or maternal or fetal tachycardia." **Exclusion criteria:** women receiving antibiotics no less than 7 days before enrollment, or with allergy to penicillin, ampicillin, gentamicin, or clindamycin; participants with a diagnosis of insulin-dependent diabetes, connective tissue disorder, or a positive human immunodeficiency virus test; impaired renal function **Setting:** Study was conducted at 2 institutions: University of Louisville Hospital (site A), Louisville, Kentucky, and Indiana University, Wishard Memorial Hospital (site B), Indianapolis, Indiana. Conducted in the USA Study period: May 1992 through May 1996. N = 116.
Interventions	Women with a clinical diagnosis of chorioamnionitis treated with ampicillin during labor and who required cesarean delivery for obstetric indications received preoperative IV clindamycin and gentamicin and were randomly assigned to 2 groups Group 1 (n = 61) received no scheduled postoperative antibiotics Group 2 (n = 55) continued to receive clindamycin 900 mg every 8 hours and gentamicin 1.5 mg/kg every 8 hours until afebrile for a minimum of 24 hours (temperature 100°F)
Outcomes	Postpartum endometritis. Duration of fever. Length of stay. Neonatal sepsis. "All study patients were scheduled to return to the postpartum clinic 6 weeks after hospital discharge. The neonatal records were reviewed." Diagnosis of endomyometritis was defined as "an oral temperature of 101.3°F on 2 occasions 4 hours apart exclusive of the first 24 hours postpartum or a temperature of 102.2°F at any time with any of the following: fundal tenderness, adnexal tenderness, purulent lochia, or an elevated white blood cell count.3." Endometrial cultures were also collected
Notes	Identical protocol was used at both institutions. During study period, principal investigator relocated from Louisville to Indianapolis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated set of random numbers.

Turnquest 1998 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes opened in consecutive order.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not performed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/104 (Site A) and 4/26 (Site B) were excluded from analysis. "Three patients, 2 assigned to group 1 and 1 assigned to group 2, were excluded because of protocol violations. These women received the incorrect antibiotic regimen for the group to which they were assigned. One woman assigned to group 2 was delivered vaginally after enrollment. Six subjects were excluded because the data forms were misplaced after randomization. Ninety-four patients remained eligible for statistical analysis."
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgment. Although no protocol was available, study author reported main maternal and neonatal outcomes
Other bias	Low risk	No other biases were noted.

g: gram
IV: intravenous
kg: kilogram
mg: milligram
SD: standard deviation
vs: versus
ºC: degree of Celsius
ºF: degree of Fahrenheit

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

Study	Reason for exclusion
Budanov 2000	Not a randomized controlled trial.
Creatsas 1980	Healthy pregnant women; investigation of antibiotic concentrations

(*Continued*)

La-Bella 1996	Tested antibiotic postpartum treatment for intra-amniotic infection. No criteria are listed to define the diagnosis of intra-amniotic infection. Outcome data not provided.
McCredie 1956	Not randomized: strict alternation.
Rocha 1999	Randomized controlled trial that evaluates whether prophylactic use of ampicillin could avoid or reduce maternal and perinatal infectious morbidity caused by premature rupture of membranes. Only 3 participants with chorioamnionitis were included in treatment group and 2 in placebo group. No data presented for those subgroups

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

Aziz 2009

Trial name or title	Comparison of ampicillin/sulbactam versus ampicillin/gentamicin for treatment of intrapartum chorioamnionitis: a randomized controlled trial
Methods	Randomized double-blind controlled trial.
Participants	Inclusion criteria 1. Pregnant women in labor or undergoing induction of labor. 2. 18 years of age or older. 3. Diagnosed with chorioamnionitis as defined by maternal temperature > or = 38.0 degrees Centigrade plus at least 1 of the following: maternal tachycardia (heart rate > 110), fetal tachycardia (fetal heart rate baseline > 160), purulent amniotic fluid, uterine tenderness. Exclusion criteria 1. Allergy or adverse reaction to penicillin or ampicillin, gentamicin, or sulbactam. 2. Having received antibiotics for the treatment of preterm premature rupture of membranes or other condition within the past 7 days. 3. Acute or chronic renal disease or insufficiency (creatinine > 1.0). 4. Hearing loss. 5. Major fetal congenital anomalies or intrauterine fetal demise. 6. Neutropenia. 7. HIV. 8. Myasthenia gravis or other neuromuscular disorder.
Interventions	Ampicillin/sulbactam 3 g intravenously every 6 hours, plus intravenous normal saline placebo dose every 8 hours until 24 hours post delivery Ampicillin/gentamicin 1.5 mg/kg intravenously every 8 hours plus ampicillin 2 grams intravenously every 6 hours until 24 hours post delivery
Outcomes	Proportion of participants in each arm experiencing treatment failure as indicated by resolution of maternal infection (time frame: 24 hours after delivery)
Starting date	May 2009.

Contact information	Natali Aziz, Clinical Assistant Professor, Stanford University Stanford University School of Medicine, Stanford, California, United States, 94305
Notes	

Shanks 2012

Trial name or title	Treatment utility of postpartum antibiotics in chorioamnionitis (TUPAC)
Methods	Randomized controlled trial.
Participants	Inclusion criteria: clinical diagnosis of chorioamnionitis undergoing cesarean section for delivery. Exclusion criteria: multiple gestations, allergy to beta-lactam antibiotics. Women with estimated creatinine clearance (ClCr) less than 70 mL/min, maternal fever explained by etiology other than chorioamnionitis, inability to comply with study protocol
Interventions	Drug: postpartum antibiotics. Participants randomly assigned to this arm will receive 1 additional dose of gentamicin (1.5 mg/kg) and clindamycin (900 mg) in the postpartum setting Drug: no postpartum antibiotics. Participants randomly assigned to this arm will not receive any postpartum antibiotics after delivery. They will be managed identically to participants in the other arm in terms of chorioamnionitis (fever pre-delivery) . Groups will be managed identically if endometritis (postpartum fever) develops
Outcomes	Endometritis (time frame: 7 days postpartum). Endometritis is defined as maternal temp > 38.0°C on 2 occasions over a 4-hour period or any temperature > 39.0°C > 12 hours after delivery. Endometritis will be managed per currently accepted endometritis protocol (amp 2 g q6, gentamicin 5 mg/kg q24, clindamycin 900 mg q8)
Starting date	September 2010.
Contact information	Barnes-Jewish Hospital, St Louis, Missouri, United States, 63110 Contact: Anthony Shanks, MD; 314-362-7315 shanksa@wudosis.wustl.edu
Notes	

DATA AND ANALYSES

Comparison 3. Antibiotics versus antibiotics during labor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure (endometritis)	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.27, 2.70]
2 Initial successful response to antibiotics	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.17]
3 Maximum maternal temperature	1	125	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.45, 1.25]
4 Postpartum hemorrhage	2	163	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.76, 2.56]
5 Blood transfusion	1	125	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.27]
6 Maternal postpartum hospital stay (days)	1	125	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.43, 0.43]
7 Histologic chorioamnionitis	1	125	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.33]
8 Neonatal sepsis	2	163	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.40, 2.86]
9 Respiratory distress syndrome	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.42, 6.78]
10 Neonatal antibiotic (days)	1	125	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.37, 0.77]
11 Treatment failure	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Maternal death	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Postpartum endometritis (double vs triple therapy)	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.67, 5.14]
14 Postpartum endometritis vaginal delivery (double vs triple therapy)	1	73	Risk Ratio (M-H, Fixed, 95% CI)	9.63 [0.55, 167.95]
15 Postpartum endometritis cesarean section (double vs triple therapy)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.32, 3.10]
16 Neonatal sepsis (blood culture)	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 14.52]
17 Neonatal deaths	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.24, 8.06]
18 Intraventricular hemorrhage	1	133	Risk Ratio (M-H, Fixed, 95% CI)	4.64 [0.23, 94.90]
19 Respiratory distress syndrome	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.36, 3.47]
20 Neonatal seizures	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 14.52]

Comparison 4. Antibiotics versus no treatment during postpartum period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postpartum endometritis	1	116	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.68, 3.24]
2 Wound infection	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.45]
3 Neonatal sepsis	1	116	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.23, 5.27]
4 Neonatal death	1	116	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [0.14, 79.88]
5 Trasient tachypnea	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.19, 3.55]

Comparison 5. Antibiotics versus placebo during postpartum period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	2	288	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.77]
2 Endomyometritis	2	288	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Wound infection	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Maternal sepsis	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Readmission to hospital	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Antibiotic versus antibiotics during postpartum period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.27, 3.89]
2 Nephrotoxicity	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Length of treatment (days)	1	131	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.90, 0.30]

Comparison 7. Antibiotics (short duration) versus antibiotics (long duration) in postpartum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital stay (days)	1	292	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.64, -0.16]
2 Treatment failure (vaginal and cesarean delivery)	1	292	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.42, 4.02]
3 Treatment failure (cesarean delivery)	1	117	Risk Ratio (M-H, Fixed, 95% CI)	3.31 [0.38, 28.75]
4 Treatment failure (vaginal delivery)	2	284	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.39, 5.51]
5 Wound infection	1	292	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.17, 20.37]
6 Pelvic abscess	1	292	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [0.12, 68.24]

Comparison 8. Intrapartum versus postpartum treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum maternal temperature postpartum	1	45	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.08, 0.08]
2 Maternal postpartum hospital stay (days)	1	45	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.94, -0.06]
3 Maternal febrile days	1	45	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-2.04, -0.08]
4 Maternal bacteremia	1	45	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [0.25, 19.48]
5 Early neonatal sepsis	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.44]
6 Neonatal pneumonia or sepsis	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.95]
7 Neonatal hospital stay	1	45	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-3.31, -0.49]

CONTRIBUTIONS OF AUTHORS

1. Evelina Chapman: conceived of the review and co-ordinated development of the protocol and the review. Conceived of, designed, drafted, and wrote the review; identified references for the review background; organized retrieval of papers; performed data extraction and management, statistical analysis, and interpretation of results. Approved the final draft document.

2. Ludovic Reveiz: conceived of the review and co-ordinated development of the protocol and the review. Conceived of, designed, drafted, and wrote the review; identified references for the review background; organized retrieval of papers; performed data extraction and management, statistical analysis, and interpretation of results.

3. Eduardo Illanes: provided support in designing, drafting, and writing the review; organizing retrieval of papers; and extracting data. Provided a methodological, clinical, and policy perspective to the manuscript. Approved the final draft document.

4. Xavier Bonfill Cosp: commented on and revised the manuscript.

5. All authors approved the final version of the updated review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have used the GRADE approach in assessing the quality of evidence and have included a 'Summary of findings' table. This was not prespecified in our published protocol (Chapman 2014). We also included several outcomes that were not prespecified in our published protocol: initial successful response to antibiotics; maximum maternal temperature; postpartum hemorrhage; blood transfusion; histologic chorioamnionitis; respiratory distress syndrome; intraventricular hemorrhage; neonatal seizures; and transient tachypnea.

INDEX TERMS

Medical Subject Headings (MeSH)

*Amnion; Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Cefotetan [therapeutic use]; Chorioamnionitis [*drug therapy]; Clindamycin [therapeutic use]; Delivery, Obstetric; Drug Administration Schedule; Endometritis [etiology]; Fetal Diseases [etiology]; Gentamicins [therapeutic use]; Postpartum Period; Sepsis [etiology]; Sulbactam [therapeutic use]

MeSH check words

Female; Humans; Pregnancy