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Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections (Review)

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[Intervention Review]

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

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ABSTRACT

Background

Chorioamnionitis is more likely to occur when meconium-stained amniotic fluid (MSAF) is present. Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid. Many adverse neonatal outcomes related to MSAF result from meconium aspiration syndrome (MAS). MSAF is associated with both maternal and newborn infections. Antibiotics may be an effective option to reduce such morbidity.

Objectives

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2014).

Selection criteria

Randomised controlled trials (RCTs) comparing prophylactic antibiotics with placebo or no treatment during labour for women with MSAF.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

We included two studies with 362 pregnant women. Both studies compared ampicillin-sulbactam (N = 183) versus normal saline (N = 179) in pregnant women with MSAF. Prophylactic antibiotics appeared to have no statistically significant reduction in the incidence of neonatal sepsis (risk ratio (RR) 1.00, 95% CI 0.21 to 4.76), neonatal intensive care unit (NICU) admission (RR 0.83, 95% CI 0.39 to 1.78) and postpartum endometritis (RR 0.50, 95% CI 0.18 to 1.38). However, there was a significant decrease in the risk of chorioamnionitis (RR 0.36, 95% CI 0.21 to 0.62). No serious adverse effects were reported. Drug resistance, duration of mechanical ventilation and duration of admission to NICU/hospital were not reported. Most of the domains for risk of bias were at low risk of bias for one study and at unclear risk of bias for the other study. The quality of the evidence using GRADE was low for neonatal sepsis, postpartum endometritis, and neonatal mortality and morbidity prior to discharge (Neonatal intensive care admissions) and of moderate quality for chorioamnionitis.

Authors' conclusions

Current evidence indicates that compared to placebo, antibiotics for MSAF in labour may reduce chorioamnionitis. There was no evidence that antibiotics could reduce postpartum endometritis, neonatal sepsis and NICU admission. This systematic review identifies the need for more well-designed, adequately powered RCTs to assess the effect of prophylactic antibiotics in the incidence of maternal and neonatal complications.

PLAIN LANGUAGE SUMMARY

Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Meconium-stained amniotic fluid (MSAF) is the result of waste material from the fetal colon passing into the mother's amniotic cavity. Its incidence increases in post-term pregnancies. Pregnant women with MSAF are more likely to develop maternal complications including inflammation of the fetal membranes caused by a bacterial infection (chorioamnionitis), postpartum inflammation of the lining of the uterus (endometritis) and neonatal complications such as neonatal sepsis and the need for admission to a neonatal intensive care unit (NICU). Fetal stress or hypoxia may trigger gasping fetal respirations, which results in the aspiration of meconium.

Our review was based on two identified randomised controlled study (involving 362 women) and found that prophylactic antibiotics may reduce the risk of intra-amniotic infection in women with MSAF (*moderate quality evidence*). Antibiotics use did not clearly reduce neonatal sepsis (*low quality evidence*), NICU admission (*low quality evidence*) or postpartum endometritis (*low quality evidence*). Studies with much larger numbers of pregnant women with MSAF would be needed to examine these issues.

Summary of findings for the main comparison. Antibiotic versus placebo for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Antibiotic versus placebo for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Population: Women with meconium-stained amniotic fluid in labour, gestational age more than 24 weeks
Settings: A hospital, North Carolina, United States
Intervention: Antibiotic versus placebo for preventing maternal and neonatal infections

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic versus placebo				
Neonatal sepsis	**Study population**		**RR 1** (0.21 to 4.76)	120 (1 study)	⊕⊕⊝⊝ **low** [1]	
	50 per 1000	**50 per 1000** (10 to 238)				
	Moderate					
	50 per 1000	**50 per 1000** (10 to 238)				
Chorioamnionitis	**Study population**		**RR 0.36** (0.21 to 0.62)	362 (2 studies)	⊕⊕⊕⊝ **moderate** [2]	
	240 per 1000	**86 per 1000** (50 to 149)				
	Moderate					
	239 per 1000	**86 per 1000** (50 to 148)				
Postpartum endometritis	**Study population**		**RR 0.5** (0.18 to 1.38)	120 (1 study)	⊕⊕⊝⊝ **low** [1]	
	167 per 1000	**83 per 1000** (30 to 230)				
	Moderate					

	167 per 1000	**84 per 1000** (30 to 230)				
Mortality and morbidity prior to discharge (Neonatal intensive care admissions)	**Study population**		**RR 0.83** (0.39 to 1.78)	120 (1 study)	⊕⊕⊝⊝ **low** [1]	
	200 per 1000	**166 per 1000** (78 to 356)				
	Moderate					
	200 per 1000	**166 per 1000** (78 to 356)				
Side effects of treatment	Not estimable		0 (0 study)	See comment		This outcome was not reported in any of the included studies.
Duration of admission to neonatal intensive care unit	Not estimable		0 (0 study)	See comment		This outcome was not reported in any of the included studies.

*The basis for the **assumed risk** (e.g. the 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.

[1] Wide confidence interval crossing the line of no effect, small sample size and few events (-2).
[2] Most weight contributed by a study with design limitations (-1).

BACKGROUND

Description of the condition

Meconium-stained amniotic fluid (MSAF), as a result of the passage of fetal colonic contents into the amniotic cavity, occurs in approximately 12% of all deliveries (Cleary 1998). The incidence of intrapartum MSAF ranges from 7% to 22% for a term pregnancy but this figure increases to up to 40% in a post-term pregnancy (Katz 1992). The composition of meconium from a term fetus is primarily water (70% to 80%). Other constituents include mucopolysaccharides, cholesterol and its precursors, proteins, lipids, bile acids and salts (giving the characteristic green colour), pancreatic enzymes, interleukin-8, phospholipase A2, squamous cells, and vernix caseosa (white substance coating the skin of newborn babies) (Cleary 1998; Usta 2000).

MSAF may act directly and indirectly on exposed tissue. Its effects depend on the concentration of meconium, duration of exposure, and the presence of associated stress factors (hypoxia, infection). MSAF has long been associated with potentially adverse fetal outcomes including meconium aspiration syndrome (MAS), admission to neonatal intensive care unit (NICU), neonatal sepsis, cerebral palsy, seizure and pulmonary diseases (Berkus 1994; Katz 1992; Nathan 1994). Many adverse neonatal outcomes related to MSAF result from MAS. MAS occurs in 5% of the cases of MSAF and more than 4% of infants with MAS die, accounting for 2% of all perinatal deaths (Cleary 1998; Wiswell 1990). Hypoxia is the key factor that triggers gasping fetal respirations, which results in the aspiration of meconium. Most cases of MAS probably result from in utero aspiration rather than aspiration at the time of delivery. In addition to possibly contributing to respiratory distress in the neonate, MSAF has been associated with a higher risk of neonatal infection (Romero 1991). Chorioamnionitis is a risk factor for neonatal sepsis, which results in NICU admissions and potential fetal morbidity and death (Alexander 1999). Fetal microbial invasion has been proposed to cause inflammatory brain damage through the effects of elevated cytokines (e.g. tumour necrosis factor (TNF) alpha, IL-1 beta,and IL-6) (Hoskins 1987).

Chorioamnionitis is also more likely to occur when MSAF is present (Mazor 1995; Romero 1991; Usta 2000). The risk of clinical chorioamnionitis and histological chorioamnionitis in patients with intrapartum MSAF is significantly higher than those with clear fluid. The risk for clinically diagnosed endometritis is two-fold (Markovitch 1993; Mazor 1995). Intrapartum chorioamnionitis is associated with dystocia and increased risk for operative delivery (Casey 1997; Mark 2000). Unrecognised or under-treated chorioamnionitis can lead to postpartum endomyometritis, which can result in further maternal morbidity, and increased length of stay in hospital and hospital costs. MSAF is the risk factor for microbial invasion of the amniotic cavity in patients with intact membranes and preterm labour (Romero 1991). Maternal infection is also more likely in the presence of MSAF. Patients with MSAF were almost two and a half times as likely to develop postoperative endometritis (Josephson 1984). There are statistically significant associations between MSAF and puerperal infection in term deliveries (Piper 1998). Puerperal infection rates are associated with the degree of meconium staining, with rates rising as meconium thickness increases (Tran 2003). There is a three-fold increase in positive amniotic fluid cultures in patients with MSAF compared to those with clear amniotic fluid (Mazor 1995; Romero 1991).The most common amniotic fluid isolates in MSAF are anaerobes, *Ureaplasma urealyticum, Streptococci, Escherichia coli, Candida albicans* and *Listeria monocytogenes* (Mazor 1995; Romero 1991).

Meconium may enhance the growth of bacteria in amniotic fluid by serving as a growth factor, inhibiting bacteriostatic properties of amniotic fluid, or antagonising host defence systems, thus increasing the risk of chorioamnionitis. Generally, amniotic fluid is a poor culture medium for *Escherichia coli, Listeria monocytogenes* and *Staphylococcus aureus;* however, with enough meconium, amniotic fluid becomes an excellent culture medium (Florman 1969). Meconium may alter the zinc-to-phosphorous ratio in amniotic fluid and facilitate bacterial growth and decrease host defences (Hoskins 1987). Light and very light MSAF significantly impair mechanisms for intracellular microbial killing. The phagocytic ability of neutrophils (a type of white blood cell) was also significantly diminished in the presence of moderate MSAF (Clark 1995). Mechanisms of meconium-associated puerperal infections include altering the antibacterial properties of amniotic fluid and enhancing bacterial growth, impairing the host immune response through the inhibition of phagocytosis and neutrophil oxidative burst (Clark 1995; Katz 1992).

Description of the intervention

One study has shown a significant reduction in the rate of clinical chorioamnionitis when the intervention ampicillin-sulbactam was administered prophylactically for the indication of MSAF (Edwards 1999).

How the intervention might work

Antibiotics can be bacteriostatic (they stop bacteria from multiplying) or bactericidal (they kill the bacteria). To perform either of these functions, antibiotics must be brought into contact with the bacteria. Antibiotics are thought to interfere with the surfactant of bacteria cells, causing a change in their ability to reproduce (Heizmann 2007). Gentamicin is an aminoglycoside antibiotic with bactericidal activity that acts at the 30S bacterial ribosomal subunit, inhibiting the synthesis of bacterial proteins (Ward 2008).

Why it is important to do this review

Cochrane reviews have addressed a number of issues about MAS including steroid therapy, endotracheal intubation, surfactant and antibiotics for neonates (Halliday 2001; Shivananda 2006; Ward 2003). Other interventions include amnioinfusion for MSAF in labour (Hofmeyr 2014). Prophylactic intravenous intrapartum ampicillin-sulbactam therapy or cefazolin infusion into the amniotic cavity during amnioinfusion in mothers with MSAF did not show any benefit in reducing chorioamnionitis, endometritis and neonatal sepsis (Adair 1996; Edwards 1999). However, the role of antibiotics for MSAF during labour has not been systematically evaluated.

OBJECTIVES

The objective of this review is to assess the efficacy and side effects of prophylactic antibiotics for meconium-stained amniotic fluid during labour in preventing maternal and neonatal infections.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of prophylactic antibiotic administration during labour for women with MSAF. We excluded quasi-RCTs. Conference abstracts were considered eligible for inclusion.

Types of participants

Pregnant women with a gestational age of more than 22 weeks who were in labour and had MSAF.

Types of interventions

Systemic prophylactic antibiotics started during labour in women with MSAF compared with no treatment or placebo.

Types of outcome measures

The primary outcomes were the most clinically important for the neonate, whereas the secondary outcomes also included maternal and neonatal complications.

Primary outcomes

1. Neonatal sepsis.

(Definition of sepsis as defined by authors.)

Secondary outcomes

Maternal

1. Intrapartum chorioamnionitis.
2. Postpartum endometritis.
3. Side effects of treatment, e.g. drug allergy, anaphylactic shock.
4. Drug resistance.

Neonatal

1. Mortality and morbidity prior to discharge, e.g. birth asphyxia, intracranial haemorrhage, intraventricular haemorrhage, necrotising enterocolitis and admission to neonatal intensive care unit (NICU).
2. Duration of mechanical ventilation (days).
3. Duration of admission to NICU/hospital.

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 searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 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;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
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.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, please refer to Siriwachirachai 2010.

For this update (2014), the following methods were used for full 'Risk of bias' assessment and assessment of the quality of evidence using the GRADE approach.

Selection of studies

Thitiporn Siriwachirachai (TS) and Ussanee Sangkomkamhang (US) independently assessed trials for inclusion and methodological; quality. There were no disagreements.

Data extraction and management

We designed a form to extract data. For eligible studies, TS and US independently extracted the data using the agreed form. There were no discrepancies. We entered the data into Review Manager software (RevMan 2014) and checked for accuracy. We did not contact the original study authors because the reported information was sufficient in the report.

Assessment of risk of bias in included studies

TS and US independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

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

We described for the one 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, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

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

We described for the included study the method used to conceal allocation to interventions prior to 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 (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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

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

We assessed the methods as:

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

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

We described for the 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 amount, nature and handling of incomplete outcome data)

We described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

We described for the 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 (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

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

(7) Overall risk of bias

We made explicit judgements about whether the one included study was at high risk of bias, according to the criteria given in the *Cochrane Handbook of Reviews of Intervention* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

For this update the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following the outcomes.

1. Neonatal sepsis
2. Intrapartum chorioamnionitis.
3. Postpartum endometritis.
4. Side effects of treatment, e.g. drug allergy, anaphylactic shock.
5. Mortality and morbidity prior to discharge, e.g. birth asphyxia, intracranial haemorrhage, intraventricular haemorrhage, necrotising enterocolitis and admission to NICU.
6. Duration of admission to NICU/hospital.

Although, we could not assess some outcomes listed due to lack of data, we were able to asses neonatal sepsis, chorioamnionitis, and postpartum endometritis.

GRADE profiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. In future updates, if more studies are included a summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach.

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The 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 (RR) with 95% confidence intervals (CIs) .

Continuous data

For continuous data, we planned to use the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We included only one randomised controlled trial (RCT). In future updates, if we identify cluster-randomised trials, we will include these in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using 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 (Higgins 2009). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and we consider the interaction between the effect of intervention and the choice of randomisation unit to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For the included study, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis; i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in the included trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

This review did not include meta-analysis. In future updates, as more data become available, we will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if a Tau^2 is greater than zero and either an I^2 is greater than 30% or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In subsequent updates of this review, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) 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 it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). This review only included one RCT so we did not pool any data. In future updates, if more data become available, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, when sufficient data become available, we plan to carry out the following subgroup analyses:

1. intact versus rupture membrane;
2. single versus combine antibiotic regimens;
3. duration of antibiotics less than 24 hours versus more than 24 hours.

We will use the following outcomes in subgroup analysis:

- early onset neonatal sepsis (symptomatic before 72 hours of age);
- late onset neonatal sepsis (symptomatic after 72 hours of age).

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

Sensitivity analysis

In subsequent updates we also plan to conduct a sensitivity analysis to compare the results using all studies and using only those of high methodological quality, i.e. comparing studies at low risk of bias versus high risk of bias.

RESULTS

Description of studies

Results of the search

We identified four publications as potentially eligible for inclusion in this review.

Included studies

This review includes two RCT (Adair 1996; Adair 1999) in which 362 women were randomised and the results analysed; *see* Characteristics of included studies.

Excluded studies

We assessed and excluded two retrospective cohort studies (Adair 1998; Edwards 1999); *see* Characteristics of excluded studies.

Risk of bias in included studies

We have summarised the risk of bias of the included studies (Adair 1996; Adair 1999) in Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

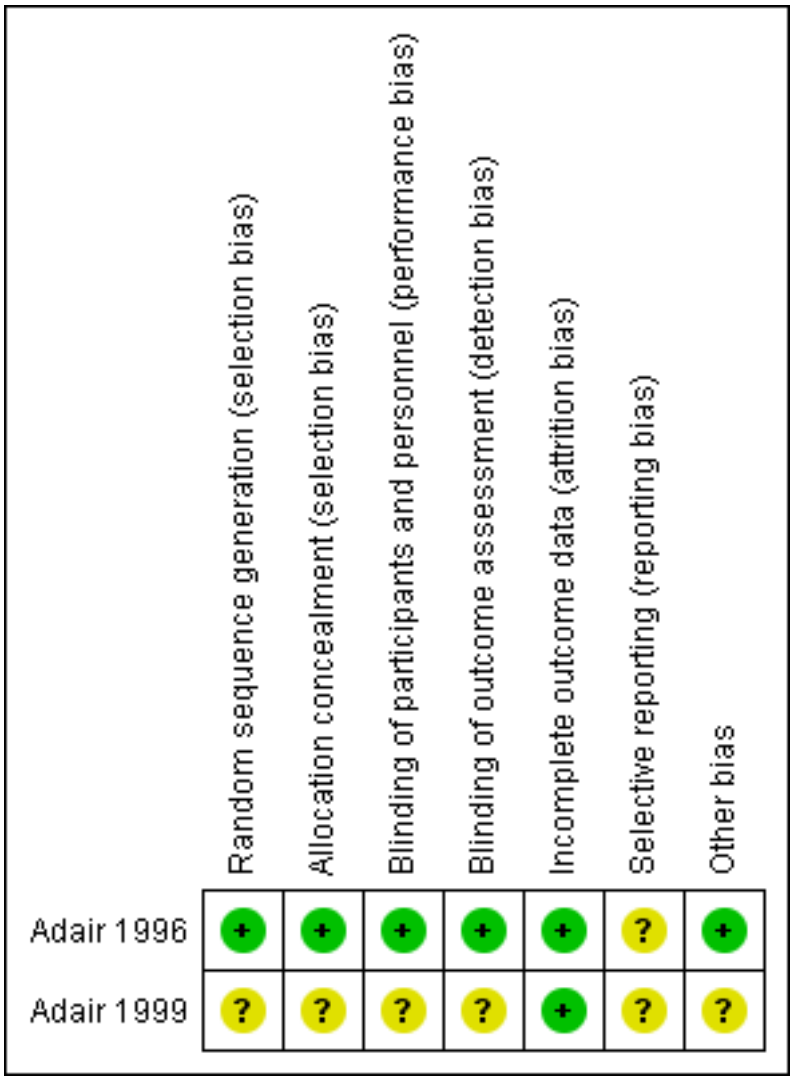
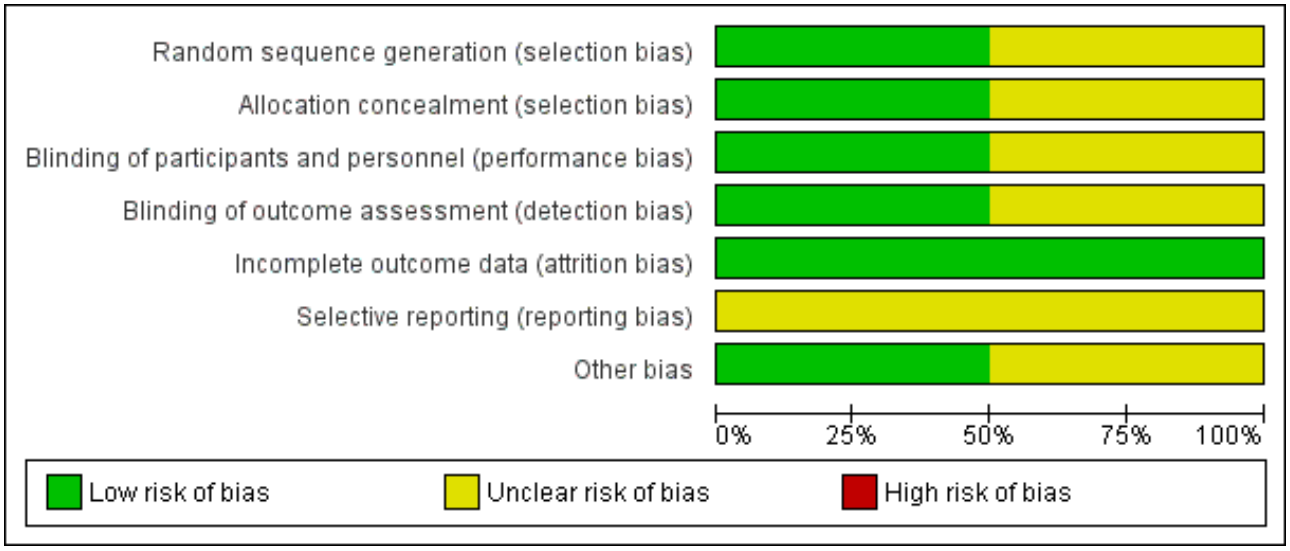


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

One trial reported clear information on allocation concealment. The randomisation schedule was generated and kept in an area away from the clinical area and was unavailable to caregivers (Adair 1996). Another trial, published as a conference abstract contained little information and so it was unclear how randomisation and allocation concealment had been performed (Adair 1999).

Blinding

Adair 1996 reported participants and all caregivers were thoroughly blinded until the study was completed. Interventions were identically prepared in 100 mL fluid bags and issued by one of two research nurses, independent to the trial investigators. The outcome assessors were also blinded to the randomisation status. The other trial report did not contain enough information to be able tell whether blinding had been undertaken (Adair 1999).

Incomplete outcome data

Two trials (Adair 1996; Adair 1999) reported no withdrawals. Adair 1996 reported analysis based on intention-to-treat basis.

Selective reporting

We do not have access to this study protocol; therefore we could not evaluate this risk of bias.

Other potential sources of bias

None apparent in one study (Adair 1996); and unclear in the other study published in abstract form (Adair 1999).

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic versus placebo for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections

Results are based on two randomized controlled trials (362 women).

Antibiotic versus placebo

Primary outcomes

There was no significant reduction in the incidence of neonatal sepsis (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.21 to 4.76; one study; 120 women), *see* Analysis 1.1. Adair 1996 did not report their results in terms of early and late onset neonatal sepsis.

Secondary outcomes

There was a significant reduction in the incidence of chorioamnionitis in the ampicillin-sulbactam group compared with placebo (RR 0.36, 95% CI 0.21 to 0.62; two studies; 362 women), *see* Analysis 1.2. There was no significant reduction in the incidence of endometritis (RR 0.50, 95% CI 0.18 to 1.38; one study; 120 women), *see* Analysis 1.3 or neonatal intensive care unit (NICU) admission (RR 0.83, 95% CI 0.39 to 1.78; one study; 120 women), *see* Analysis 1.4.

No serious adverse effects were reported. Drug resistance, duration of mechanical ventilation and duration of admission to NICU/ hospital were not reported

DISCUSSION

Summary of main results

There was a significant reduction in the incidence of chorioamnionitis in mothers who received ampicillin-sulbactam compared to placebo. Neonatal sepsis was not differentiated into 'early' or 'late' onset but there was no difference in the incidence of neonatal sepsis between the two groups. Endometritis was not statistically reduced. There was no information about adverse effects.

Overall completeness and applicability of evidence

Two randomised controlled trials (RCT) from a developed country were included in this review and they did not report the primary outcome 'neonatal sepsis' in terms of early or late onset. The evidence may be insufficient to evaluate the efficacy and side

effects of prophylactic antibiotics for meconium-stained amniotic fluid in labour for preventing neonatal sepsis.

Quality of the evidence

Most of the domains for risk of bias were at low risk of bias for one study (Adair 1996) and at unclear risk of bias for the other study (Adair 1999). The quality of the evidence using GRADE was low for neonatal sepsis, postpartum endometritis, and neonatal mortality and morbidity prior to discharge (Neonatal intensive care admissions) and of moderate quality for chorioamnionitis. No serious adverse effects were reported. Drug resistance, duration of mechanical ventilation and duration of admission to NICU/hospital were not reported.

Potential biases in the review process

We followed the process of review as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2009. We also did an exhaustive search which included many clinical trial registries.

Agreements and disagreements with other studies or reviews

There are no other reviews and studies related to the efficacy and side effects of prophylactic antibiotics for MSAF during labour in preventing maternal and neonatal infections.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of prophylactic antibiotics in women with meconium-stained amniotic fluid (MSAF) during labour because the rates of neonatal sepsis were not different in the two groups.

Implications for research

This systematic review has identified the need for more well-designed, adequately powered RCTs to assess the benefits and harms of antibiotic prophylactic in MSAF during labour for preventing neonatal sepsis. The trials should include clinical outcomes of neonatal sepsis for both early onset neonatal sepsis (symptomatic before 72 hours of age) and late onset neonatal sepsis (symptomatic after 72 hours of age).

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CHARACTERISTICS OF STUDIES

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

Adair 1996

Methods	Randomised trial with allocation concealment using computer-generated randomisation list. All participants, caregivers and outcome assessors were blinded to the treatment regimen.
Participants	**Intervention group:** 60 pregnant women (mean age 24.5, SD 6.3) with gestational age more than 24 weeks (mean 39.8, SD 1.0). **Control group:** 60 pregnant women (mean age 25.9, SD 6.3), (mean gestational age 39.9, SD 1.2). **Inclusion criteria:** gestational age more than 24 weeks with MSAF complicating the intrapartum. **Exclusion criteria:** women with penicillin and/or cephalosporin allergy, evidence of active infection, presence of intrauterine death, GA < 24 weeks, or history of antibiotics use in 7 days. **Location:** North Carolina, United States.

Adair 1996 *(Continued)*

Interventions	**Intervention**: ampicillin-sulbactam 3.0 g intravenous prepared in 100 mL fluid bags, and was repeated every 6 hours until delivery. **Control**: normal saline infused as an IV bolus.
Outcomes	**Mother** Chorioamnionitis. Postpartum endometritis. **Neonatal** Number of NICU admissions. Incidence of sepsis (not defined), and adverse outcomes including enterocolitis and respiratory distress.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated list.
Allocation concealment (selection bias)	Low risk	Adequate: there was randomisation by computer-generated list and both IV preparations were prepared by 1 of 2 research nurses who were not involved in this study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate: ampicillin-sulbactam and normal saline were identically prepared. Both preparations were prepared by research nurses who were not involved in the clinical care of the women.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate: all caregivers were blinded to the randomisation status of the woman.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate: there were no withdrawals.
Selective reporting (reporting bias)	Unclear risk	Unclear, because we do not have access to this trial's protocol.
Other bias	Low risk	Study appeared to be free of other sources of bias.

Adair 1999

Methods	No information of randomisation, allocation concealment and blinding.
Participants	**Intervention group:** 123 pregnant women (mean age 24.8, SD 3.7), (mean gestational age 39.8, SD 1.9) with intrapartum diagnosis of MSAF. **Control group:** 119 pregnant women (mean age 23.4, SD 3.4), (mean gestational age 39.8, SD 1.1) with intrapartum diagnosis of MSAF. **Inclusion criteria:** absence of obvious infection, temperature < 100 F, MSAF passage and willingness to participate.

Adair 1999 *(Continued)*

	Exclusion criteria: fetal heart rate > 180, penicillin or cephalosporin allergy.
Interventions	**Intervention**: ampicillin-sulbactam 3.0 g intravenous. **Control**: normal saline.
Outcomes	Intra- amniotic infection.
Notes	Data from conference abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow up.
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	Not described.

GA: gestational age
IV: intravenous
MSAF: meconium-stained amniotic fluid
NICU: neonatal intensive care unit
RCT: randomised controlled trial
SD: standard deviation

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

Study	Reason for exclusion
Adair 1998	Not a RCT, this was a retrospective cohort study.
Edwards 1999	Intervention not of interest to systematic review; not systematic prophylactic antibiotics.

RCT: randomised controlled trial

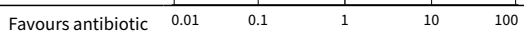
DATA AND ANALYSES

Comparison 1. Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal sepsis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.76]
2 Chorioamnionitis	2	362	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.21, 0.62]
3 Postpartum endometritis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.18, 1.38]
4 Neonatal intensive care admissions	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.39, 1.78]

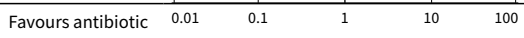
Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Neonatal sepsis.

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Adair 1996	3/60	3/60		100%	1[0.21,4.76]
Total (95% CI)	**60**	**60**		**100%**	**1[0.21,4.76]**
Total events: 3 (Antibiotic), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



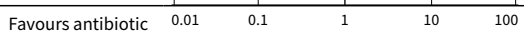
Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Chorioamnionitis.

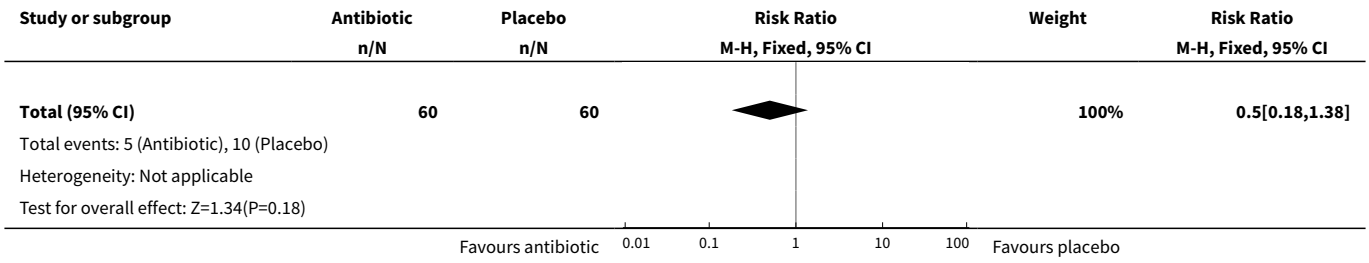
Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Adair 1996	4/60	14/60		32.2%	0.29[0.1,0.82]
Adair 1999	12/123	29/119		67.8%	0.4[0.21,0.75]
Total (95% CI)	**183**	**179**		**100%**	**0.36[0.21,0.62]**
Total events: 16 (Antibiotic), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=3.7(P=0)					



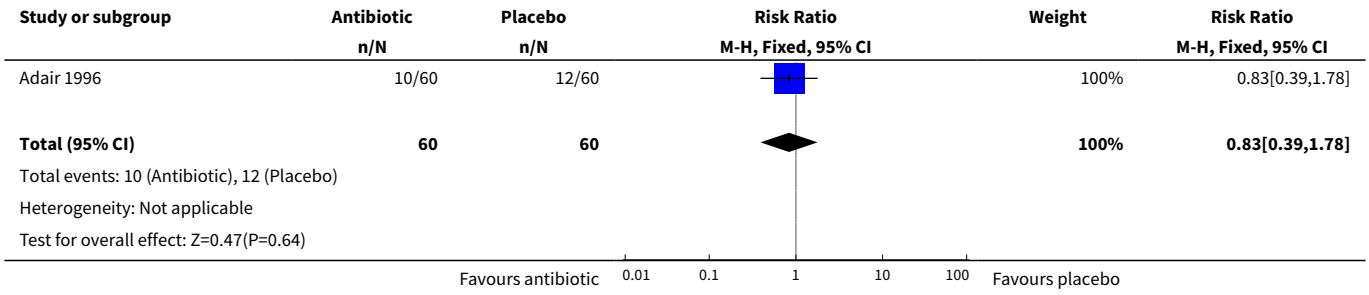
Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Postpartum endometritis.

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Adair 1996	5/60	10/60		100%	0.5[0.18,1.38]





Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Neonatal intensive care admissions.



WHAT'S NEW

Date	Event	Description
30 September 2014	New citation required but conclusions have not changed	Review updated.
30 September 2014	New search has been performed	Updated search and methods. No new trials identified. 'Summary of findings' table incorporated. One previously excluded study (Adair 1999) is now included.

HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 12, 2010

Date	Event	Description
18 January 2012	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Thitiporn Siriwachirachai and Ussanee Sangkomkamhang drafted the review, Pisake Lumbiganon and Malinee Laopaiboon revised and approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Amniotic Fluid; *Labor, Obstetric; *Meconium; Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Chorioamnionitis [*prevention & control]; Endometritis [prevention & control]; Intensive Care Units, Neonatal [statistics & numerical data]; Randomized Controlled Trials as Topic; Sepsis [prevention & control]; Sulbactam [therapeutic use]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy