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Comunián-Carrasco G, Peña-Martí GE, Martí-Carvajal AJ.
Antibiotics for treating gonorrhoea in pregnancy.
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD011167.
DOI: [10.1002/14651858.CD011167.pub2](https://doi.org/10.1002/14651858.CD011167.pub2).

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[Intervention Review]

Antibiotics for treating gonorrhoea in pregnancy

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Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New, published in Issue 2, 2018.

Citation: Comunián-Carrasco G, Peña-Martí GE, Martí-Carvajal AJ. Antibiotics for treating gonorrhoea in pregnancy. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD011167. DOI: [10.1002/14651858.CD011167.pub2](https://doi.org/10.1002/14651858.CD011167.pub2).

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ABSTRACT

Background

Gonorrhoea is a sexually transmitted infection that is caused by *Neisseria gonorrhoeae*, and is a major public health challenge today. *N gonorrhoeae* can be transmitted from the mother's genital tract to the newborn during birth, and can cause gonococcal ophthalmia neonatorum as well as systemic neonatal infections. It can also cause endometritis and pelvic sepsis in the mother. This review updates and replaces an earlier Cochrane Review on antibiotics for treating this infectious condition.

Objectives

To assess the clinical effectiveness and harms of antibiotics for treating gonorrhoea in pregnant women.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 May 2017), LILACS database (1982 to April 5, 2017), the WHO International Clinical Trials Registry Platform (ICTRP; April 5, 2017), ClinicalTrials.gov (April 5, 2017), the [ISRCTN Registry](http://ISRCTN.org) (April 5, 2017), and [Epistemonikos](http://Epistemonikos.org) (April 5, 2017). We also searched reference lists of all retrieved articles.

Selection criteria

We included randomised controlled trials (RCTs) comparing the use of antibiotics for treating gonorrhoea in pregnancy. The antibiotics could have been used alone or in combination, were administered parenterally, orally, or both, and were compared with another antibiotic.

We included RCTs regardless of their publication status (published, unpublished, published as an article, an abstract, or a letter), language, or country. We applied no limits on the length of follow-up.

We excluded RCTs using a cluster- or cross-over design, or quasi-RCTs.

Data collection and analysis

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

Main results

We included two RCTs, that randomised 514 pregnant women (347 women analysed) at a mean gestational age of 22 weeks. Both trials were conducted in the outpatient department of the same two hospitals in the USA between 1993 and 2001, and had a follow-up of 14 days. One of the trials was sponsored by a drug company. We considered both trials to be at a high risk of bias.

One trial compared ceftriaxone (125 mg, intramuscular) with cefixime (400 mg, oral); the other trial had three arms, and assessed ceftriaxone (250 mg, intramuscular) versus either amoxicillin (3 g, oral) plus probenecid (1 g, oral) or spectinomycin (2 g, intramuscular). We did not include the spectinomycin data because this medication is no longer produced. We were unable to conduct meta-analysis because the trials compared different medications.

We found inconclusive evidence that there were clear differences in the cure of gonococcal infections (genital, extragenital, or both) between intramuscular ceftriaxone versus oral amoxicillin plus oral probenecid (risk ratio (RR) 1.07, 95% confidence interval (CI) 0.98 to 1.16; one RCT; 168 women; very low-quality evidence) or intramuscular ceftriaxone versus oral cefixime (RR 0.99, 95% CI 0.91 to 1.08; one RCT; 95 women; very low-quality evidence).

Neither of the trials reported on two of this review's primary maternal outcomes: incidence of obstetric complications (miscarriage, premature rupture of membranes, preterm delivery, or fetal death), or disseminated gonococcal infection, or on the incidence of neonatorum ophthalmia in the neonates.

One trial reported one case of vomiting in the oral amoxicillin plus probenecid group. Trials reported pain at the injection sites, but did not quantify it. Hyperbilirubinemia was more frequent in neonates whose mothers were exposed to ceftriaxone. There were no clear differences between groups for neonatal malformation.

Authors' conclusions

This Cochrane Review found high levels of cure of gonococcal infections in pregnancy with the given antibiotic regimens. However, the evidence in this review is inconclusive as it does not support one particular regimen over another. This conclusion was based on very low-quality evidence (downgraded for poor trial design, imprecision) from two trials (involving 514 women), which we assessed to be at a high risk of bias for a number of domains. The harm profiles of the antibiotic regimes featured in this review remain unknown.

High-quality RCTs are needed, with sufficient power to assess the clinical effectiveness and potential harms of antibiotics in pregnant women with gonorrhoea. These should be planned according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), conducted following CONSORT recommendations, and based on Patient-Centered Outcomes Research Institute (PCORI) outcomes.

PLAIN LANGUAGE SUMMARY

Antibiotics for treating gonorrhoea in pregnancy

What is the question?

Gonorrhoea is an infection caused by the *Neisseria gonorrhoeae* bacteria, and is a major public health challenge. It is most frequently spread during sexual contact (i.e. vaginal intercourse, oral sex, or anal sex), but can also spread from a pregnant woman to her baby during delivery. Women often do not have any symptoms of gonorrhoea. The gonorrhoea organisms can spread (disseminate) from an initial local site into the blood and cause infection of other organs. Symptoms of disseminated gonococcal infection include rash, fever, joint pain, infection of joints, and inflammation of tendons, the inner lining of the heart (endocarditis), and the membranes covering the brain and spinal cord (meningitis). We reviewed the clinical effectiveness and adverse effects of antibiotics for treating gonorrhoea in pregnant women.

This review updates and replaces an earlier Cochrane Review on this topic.

Why is this important?

Gonorrhoea can cause problems for both the pregnant woman and her baby. It is associated with preterm delivery, pre-labour rupture of the membranes, low birthweight, and inflammation of the inner lining of the uterus (endometritis) after giving birth. Babies can become infected during birth, and occasionally by the spread of the infection before birth, when the membranes rupture too early before birth. This can result in eye infections (ophthalmia neonatorum - an eye infection contracted during birth) as the baby passes through the birth canal.

What did we find?

We searched for evidence in April 2017 and found two randomised controlled trials, conducted in outpatient departments of the same two hospitals in the USA, between 1993 and 2001. One trial was sponsored by a drug company. The trials randomised a total of 514 pregnant women (347 women analysed), at an average gestational age of 22 weeks. Both trials had a follow-up of 14 days.

We were unable to pool the results because the trials used different comparisons. One trial compared ceftriaxone (125 mg, intramuscular) with cefixime (400 mg, oral), and the other trial assessed a higher dose of ceftriaxone (250 mg, intramuscular) versus either amoxicillin (3 g, oral) plus probenecid (1 g, oral) or spectinomycin (2 g, intramuscular). We did not include data from the spectinomycin group because this medication is no longer produced.

We found no clear difference in the rate of cure of gonococcal infection (both genital and unrelated to the genital organs) for the different treatment groups, which was in the order of 89% to 96% (very low-quality evidence).

Trials did not report on the incidence of obstetric complications, disseminated gonococcal infection in the mother, or ophthalmia neonatorum in the baby.

They provided little information on side effects of the antibiotic regimens. One trial reported one case of vomiting in the oral amoxicillin plus probenecid group. Trials reported pain at the injection sites, but did not report numbers or severity. Hyperbilirubinemia (where the baby has too much bilirubin in the blood) was more frequent in newborns whose mothers were exposed to ceftriaxone. There was no clear difference between groups for neonatal malformation.

What does this mean?

We found high levels of cure of gonococcal infection in pregnancy with the given antibiotic regimens, but there was not enough evidence to support one particular regimen over another.

Despite high levels of cure, our confidence in the results of this review is very low because both included trials were small, did not blind women to which treatment they received, and had a high number of withdrawals (28% and 41%), meaning they were at high risk of bias. Therefore, there is a need for high-quality trials to be conducted to assess the clinical effectiveness and potential harms of antibiotics for treating gonorrhoea in pregnancy women.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Intramuscular ceftriaxone compared with oral amoxicillin plus oral probenecid for treating gonorrhoea in pregnancy

Intramuscular ceftriaxone compared with oral amoxicillin plus oral probenecid

Patient or population: pregnant women with gonorrhoea infection

Settings: out-patients departments at Dallas County Hospital District and Parkland Memorial Hospital (both in Texas, USA)

Intervention: intramuscular ceftriaxone (250 mg)

Comparison: oral amoxicillin (3 g) plus oral probenecid (1 g)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral amoxicillin (3 g) plus oral probenecid (1 g)	Intramuscular ceftriaxone (250 mg)				
Cure of gonococcal infection (microbiological culture) Follow-up: 14 days	893 per 1000¹	955 per 1000 (875 to 1000)	RR 1.07 (0.98 to 1.16)	168 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	
Incidence of obstetric complications	see comment	see comment	not estimable	168 (1 study)	see comment	not assessed
Incidence of disseminated gonococcal infection	see comment	see comment	not estimable	168 (1 study)	see comment	not assessed
Neonatorum ophthalmia	see comment	see comment	not estimable	168 (1 study)	see comment	not assessed
Adverse events including treatment-related adverse events Follow-up: 14 days	12 per 1000⁵	4 per 1000 (0 to 96)	RR 0.33 (0.01 to 8.07)	168 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	vomiting after amoxicillin plus probenecid reported in 1 woman pain at the injection site reported but not quantified

no differences found between groups in neonatal malformations (major, minor, or both)

*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 Assumed risk estimated on control risk (89.3%).

² Downgraded 1 level due to limitations in the trial design or execution (uncertain allocation concealment, and open label).

³ Downgraded 2 levels due to imprecision (very low sample and number of events with an impact in the precision of the effect estimates).

⁴ Assumed risk estimated on control risk (8.3%).

⁵ Assumed risk estimated on control risk (1.3%).

Summary of findings 2. Intramuscular ceftriaxone compared with oral cefixime for treating gonorrhoea in pregnancy

Intramuscular ceftriaxone compared with oral cefixime

Patient or population: pregnant women with gonorrhoea infection

Settings: out-patients departments at Dallas County Hospital District and Parkland Memorial Hospital (both in Texas, USA)

Intervention: intramuscular ceftriaxone (125 mg)

Comparison: oral cefixime (400 mg)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral cefixime (400 mg)	Intramuscular ceftriaxone (125 mg)				
Cure of gonococcal infection (microbiological culture) Follow-up: 14 days	962 per 1000¹	952 per 1000 (875 to 1000)	RR 0.99 (0.91 to 1.08)	95 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	

Incidence of obstetric complications	see comment	see comment	not estimable	95 (1 study)	see comment	not assessed
Incidence of disseminated gonococcal infection	see comment	see comment	not estimable	95 (1 study)	see comment	not assessed
Neonatorum ophthalmia	see comment	see comment	not estimable	95 (1 study)	see comment	not assessed
Adverse events including treatment-related adverse events Follow-up: 14 days	see comment	see comment	not estimable	95 (1 study)	see comment	pain at the injection site reported but not quantified Neonatal hyperbilirubinaemia reported more frequently in neonates whose mothers had ceftriaxone ⁴ , but not quantified. no differences found between groups in neonatal malformations (major, minor, or both)

*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 Assumed risk estimated on control risk (96.2%).

² Downgraded 1 level due to limitations in the trial design or execution (uncertain allocation concealment, and open label).

³ Downgraded 2 levels due to imprecision (low sample and number of events with an impact in the precision of the effect estimates).

⁴ The women who received streptomycin were excluded from this review's analyses, but adverse events were reported in the published paper.

BACKGROUND

This Cochrane Review updates and replaces a previous Cochrane Review on the same topic (Brocklehurst 2002).

Description of the condition

Gonorrhoea is a bacterial infection caused by *Neisseria gonorrhoeae* (Hill 2016), and is a major public health challenge today, due to its high incidence (WHO 2012; WHO 2016). These infections represent 106 millions of the estimated 498 million new cases of curable sexual transmitted infections that occur globally every year (WHO 2012). Gonorrhea rates among women have been slightly higher than those among men since 2001. During 2011 to 2012, the gonorrhoea rate among women increased 0.6% to 108.7 cases per 100,000 population (CDC 2016). In women from USA, the estimated number of incidents of gonorrhoea was 354,000 in 2008 (Satterwhite 2013).

Gonorrhoea is most frequently spread during sexual contact, however, it can be also transmitted from the mother's genital tract to the newborn during birth, resulting in ophthalmia neonatorum and systemic neonatal infection (Marrazzo 2015; WHO 2016). Gonorrhoea is often asymptomatic in women. The cervix is the most common site of gonorrhoea, resulting in endocervicitis and urethritis, which can be complicated by pelvic inflammatory disease (Kreisel 2017; WHO 2016). Gonorrhoea can also spread throughout the body, and cause localised and disseminated disease (WHO 2016). Gonorrhoea is a major cause of serious reproductive complications in women (Marrazzo 2015).

The clinical pattern of gonorrhoea in pregnant women is similar to non-pregnant women; up to 45% of cases are asymptomatic (Mullick 2005).

Complications in females

The most frequent complications of gonorrhoea in females are disseminated gonococcal infection (meningitis, pericarditis, endocarditis, and acute perihepatitis, also called Fitz-Hugh-Curtis syndrome), pelvic inflammatory disease, and arthritis (Ison 2011; Marrazzo 2015; Peterman 2016; Stefanelli 2011). Women with disseminated gonococcal infection may present with symptoms of rash, fever, arthralgias (joint pain), migratory polyarthritis, septic arthritis, tendonitis, tenosynovitis, endocarditis, or meningitis (Marrazzo 2015). *N gonorrhoeae* organisms spread from a primary site, such as the endocervix, the urethra, the pharynx, or the rectum, and disseminate via the blood to infect other end organs (WHO 2016).

Complications in pregnant women

Gonorrhoea during pregnancy is associated with preterm delivery, prelabour rupture of the membranes, low birthweight, and postpartum endometritis (WHO 2005).

Complications in neonates

Neonates are infected during delivery, and occasionally prior to delivery, when the infection spreads after prolonged rupture of the membranes. Gonococcal ophthalmia neonatorum, manifesting as purulent bilateral conjunctivitis, is the most common manifestation in infants born to mothers with gonococcal genital tract infections (Marrazzo 2015; WHO 2016; Woods 2005). Localised gonococcal infection of the scalp can result from fetal monitoring, through

the scalp electrodes (Workowski 2010). Occasionally, the infection spreads, causing sepsis, arthritis, or meningitis (Heather 2007).

See Appendix 1 for medical glossary.

Description of the intervention

1. Clinical pharmacology and microbiological spectrum

Antimicrobial drugs have been suggested for the treatment of gonorrhoea; recommended regimens include beta-lactam antibiotics (third-generation cephalosporin) and macrolides (azithromycin (CDC 2015; Brunton 2018)).

1.1 Third-generation cephalosporins

Several cephalosporins are recommended for treating gonorrhoea infection. Classification by generations is based on general features of antimicrobial activity (Andes 2005). Cephalosporins are similar to penicillins, but more stable to many bacterial lactamases and therefore, have a broader spectrum of activity. Third-generation agents include cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, cefdinir, cefditoren pivoxil, ceftibuten, and moxalactam (Deck 2012).

1.2 Macrolides

Clarithromycin and azithromycin are semi-synthetic derivatives of erythromycin. Azithromycin is useful in the treatment of sexually transmitted diseases, especially during pregnancy, when tetracyclines are contraindicated. It is effective against gram-negative organisms such as *N gonorrhoeae* (Deck 2009).

2. Antibiotic adverse reactions

The major adverse reactions associated with the main antimicrobial drugs for treating gonorrhoea have been widely described (Granowitz 2008). Briefly, untoward reactions of these drugs include following.

2.1. Beta-lactam antibiotics: this group causes the most drug hypersensitivity reactions (Brunton 2018; Torres 2010). However, beta-lactams are generally safe drugs (Lagace-Wiens 2012; Petri 2001). Serious adverse events are rare, and allergies are over-diagnosed (Lagace-Wiens 2012). Cephalosporin reactions appear to be identical to those caused by the penicillins, perhaps related to the shared lactam structure of both groups of antibiotics. Immediate reactions, such as anaphylaxis, bronchospasm, and urticaria are observed. More commonly, maculopapular rash develops, usually after several days of therapy; this may, or may not be accompanied by fever and eosinophilia (Brunton 2018).

2.2. Oral macrolides are associated with anorexia, nausea, vomiting, and diarrhoea. Gastrointestinal intolerance is due to a direct stimulation of gut motility. Other allergic reactions include fever, eosinophilia, and rashes (Deck 2009).

How the intervention might work

The pharmacodynamics of antimicrobial drugs most frequently used for treating gonorrhoea in pregnant women include the following.

1. Beta-lactam antibiotics act by inhibiting the synthesis of the bacterial peptidoglycan cell wall, which is essential for their normal growth and development (Brunton 2018).

2. Macrolides inhibit the protein synthesis that occurs by binding to the 50S ribosomal RNA, which blocks the aminoacyl translocation reaction and formation of initiation complexes (Deck 2009).

Why it is important to do this review

This review updates and replaces an earlier Cochrane Review on this topic (Brocklehurst 2002). We conducted this review to identify any new randomised clinical trials with an updated literature search, and to update the methodology, in keeping with the new Cochrane standards (i.e. assessment of risk of bias (Higgins 2011a), and assessing the quality of the body of evidence with GRADE (Guyatt 2008; Guyatt 2008a)).

OBJECTIVES

To assess the clinical effectiveness and harm of antibiotics for treating gonorrhoea in pregnant women.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials regardless of their publication status (trials may be unpublished or published as an article, an abstract, or a letter), language, and country. We applied no limits to the period of follow-up.

We excluded the following designs: quasi-randomised trials, trials using a cluster-randomised or cross-over design.

Types of participants

Pregnant women of any age, at any stage of pregnancy, diagnosed with gonococcal infection (genital, extragenital, or both).

Types of interventions

We included comparative trials of antibiotics (used alone or in combination), administered parenterally, orally, or both, compared with another antibiotic.

Types of outcome measures

Primary outcomes

1. Maternal

- Cure of gonococcal infection (genital, extragenital, or both), according to the definition in included trials
- Incidence of obstetric complications (miscarriage, premature rupture of membranes, preterm delivery, or fetal death)
- Incidence of disseminated gonococcal infection

2. Neonate

- Incidence of neonatorum ophthalmia

Secondary outcomes

1. Adverse events including treatment-related adverse events (TRAE; (Ioannidis 2004)). We defined TRAE as 'a response to a drug which is noxious and uninitiated, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic

functions' (Nebeker 2004). We extracted the number of patients with at least one treatment-related adverse event out of the total randomised in each study arm. We reported adverse events for either the mother or newborn.

Search methods for identification of studies

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

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (30 May 2017).

The Register is a database containing over 23,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register, including the detailed search strategies for CENTRAL, MEDLINE, Embase, and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the [Cochrane Pregnancy and Childbirth](#) in the Cochrane Library, and select the 'Specialized Register' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist, 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. monthly searches of CINAHL EBSCO;
5. handsearches of 30 journals, and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals, plus monthly BioMed Central email alerts.

Two people screen the search results, and review the full text of all relevant trial reports identified through the searching activities described above. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Trials Register. The Information Specialist searches the Trials Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections ([Included studies](#); [Excluded studies](#)).

In addition, we searched the following databases:

1. LILACS (Latin American and Caribbean Health Science Information database; 1982 to 5 April 2017; see [Appendix 2](#) for search strategy);
2. The WHO International Clinical Trials Registry Platform (ICTRP; 5 April 2017; see [Appendix 3](#) for search strategy);
3. [ISRCTN Registry](#) (5 April 2017; see [Appendix 4](#) for search strategy);
4. [ClinicalTrials.gov](#) (5 April 2017; see [Appendix 5](#) for search strategy);
5. [Epistemonikos](#) (5 April 2017; see [Appendix 6](#) for search strategy).

Searching other resources

We searched the references of all retrieved articles.

We did not apply any language or date restrictions.

Data collection and analysis

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

Selection of studies

All three review authors independently assessed, for inclusion, all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, all three review authors extracted the data using the agreed form. We resolved any disagreement through discussion. We entered data into Review Manager 5 software and checked for accuracy ([RevMan 2014](#)).

We had planned to contact authors of the original reports to provide further details if the information reported was unclear, but that was not necessary.

Assessment of risk of bias in included studies

All three review authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We resolved any disagreement by discussion.

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

For each included study, we described 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)

For each included study, we described 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)

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

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)

For each included study, we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received.

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)

For each included study, and for each outcome or class of outcomes, we described 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 re-included missing data in the analyses 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)

For each included study, we described 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 was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review had been reported);
- high risk of bias (where not all the study's pre-specified outcomes had been reported, one or more reported primary outcomes were not pre-specified, outcomes of interest were reported incompletely and so could not be used, study failed 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)

For each included study, we described any important concerns we had 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 judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias, and whether we considered it was likely to impact the findings. For future updates, we will explore the impact of the level of bias by undertaking sensitivity analyses - see [Sensitivity analysis](#).

Assessing the quality of the body of evidence using the GRADE approach

We assessed the quality of the evidence using the GRADE approach, as outlined in the GRADE handbook, in order to assess the quality of the body of evidence relating to the following outcomes (Schünemann 2013). We selected four outcomes for the main comparisons.

1. Cure of gonococcal infection (genital, extragenital, or both).
2. Incidence of obstetric complications (miscarriage, preterm rupture of membranes, preterm delivery, or fetal death).
3. Incidence of disseminated gonococcal infection.
4. Incidence of neonatal ophthalmia neonatorum.
5. Adverse events, including treatment-related adverse events (TRAE; (Ioannidis 2004)).

We used GRADEpro GDT to import data from Review Manager 5, in order to create 'Summary of findings' tables (GRADEpro GDT 2015; RevMan 2014). A summary of the intervention effect and a measure of quality for each of the above outcomes were 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 (CI).

Dealing with missing data

For included studies, we noted levels of attrition. We would have liked to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. However, the attrition was very high for both trials, and we decided to avoid this issue.

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 all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcome data were known to be missing.

Assessment of heterogeneity

We would have liked to assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 , and χ^2 statistics. We had planned to regard heterogeneity as substantial if an I^2 was greater than 30%, and either the τ^2 was greater than zero, or P was less than 0.10 in the χ^2 test for heterogeneity. We were unable to conduct meta-analyses due to different comparison groups.

Assessment of reporting biases

We were unable to assess reporting biases because we only found two trials. For future updates, 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 Review Manager 5 software, but did not combine data from the trials in meta-analyses (RevMan 2014).

If an average treatment effect across trials is considered clinically meaningful in future updates, we will use a fixed-effect model to combine data when 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 sufficient clinical heterogeneity to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use a random-effects model to produce an overall summary. We will treat the random-effects summary as the average range of possible treatment effects, and discuss the clinical implications of treatment effects differing between trials. We will present the results with 95% confidence intervals, and τ^2 and I^2 estimates.

We will not combine trials if the average treatment effect is not clinically meaningful.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity in future updates, we will investigate it using subgroup and sensitivity analyses.

We plan to carry out the following subgroup analyses for the review's primary outcomes.

- Adolescent versus non-adolescent pregnant women.
- Pregnant women with HIV/AIDS infection versus pregnant women without HIV/AIDS.
- Pregnant women with co-existing sexual transmitted infections versus pregnant women without co-existing sexual transmitted infections.
- Neonatorum ophthalmia in the babies of women who received prophylaxis versus those who did not receive prophylaxis.

We will assess subgroup differences by interaction tests available within RevMan 5 ([RevMan 2014](#)). We will report the results of subgroup analyses quoting the χ^2 and P values, and the interaction I^2 statistic value.

Sensitivity analysis

In future updates of this review, we will perform sensitivity analysis based on trial quality, separating high-quality trials from those of low quality. Furthermore, we plan to conduct a sensitivity analysis to assess attrition bias: trials with low attrition bias ($\leq 12\%$ loss to follow-up) versus trials with high attrition bias ($> 12\%$ loss to follow-up). Both trials showed very high attrition levels.

RESULTS

Description of studies

Results of the search

Our search identified 65 reports (see: [Figure 1](#)). Two randomised trials met the inclusion criteria ([Cavenee 1993](#); [Ramus 2001](#)).

Figure 1. Study flow diagram .

Included studies

We identified two trials ([Cavenee 1993](#); [Ramus 2001](#)). [Cavenee 1993](#) was associated with three reports, while [Ramus 2001](#) was associated with two reports. Both trials involved a total of 514 randomised pregnant women, but only analysed 68% (347/514) of them. The main reason for exclusions in both trials was negative pre-therapy cultures. [Cavenee 1993](#) was carried out between January 1990 and March 1992, and [Ramus 2001](#) from April 1994 to October 1997. Participants were recruited from outpatient departments of Dallas County Hospital District and Parkland Memorial Hospital, Dallas, Texas, USA.

Design

[Cavenee 1993](#) and [Ramus 2001](#) were parallel-design trials. Both trials had a follow-up of 14 days. The trials were conducted in the same academic institution and hospital located in Dallas, Texas, USA, likely by the same research team.

Sample size

Trialist carried out sample size estimation a priori. One trial was stopped early in 1997 for decreasing frequency of gonorrhoea in the patient population, which prevented them from reaching their estimated sample size ([Ramus 2001](#)).

Settings

Both trials were conducted with pregnant women from outpatient departments at Dallas County Hospital District and Parkland Memorial Hospital.

Participants

All pregnant women included in both trials came from the same location. The demographic characteristics described the analysed participants. They had a mean of age of 19.8 years; 84% were African descent, 11% were Hispanic, and 7.6% were white. [Cavenee 1993](#) reported 49.6% were nulliparous, while [Ramus 2001](#) reported neither gravidity nor parity data of the women. Both trials involving pregnant women with a mean gestational age of 22 weeks. In 252 analysed women, [Cavenee 1993](#) reported that the most frequent mucosal sites were endocervix (97%), rectum (27%), and pharynx (7%). Seventy-seven participants (31%) had infections of either the rectum or pharynx. In 95 women, [Ramus 2001](#) reported eighty-six (91%) had endocervical gonococcal infection. Forty pregnant women had concomitant gonorrhoea of either the rectum or

pharynx; 34% of the women had extragenital infection, mainly due to concomitant anal gonorrhoea.

Intervention and comparison

[Cavenee 1993](#) was a three-armed trial, [Ramus 2001](#) was a two-armed trial. Both trials assessed ceftriaxone as the experimental intervention, but the dose varied. [Cavenee 1993](#) used 250 mg/dose, while [Ramus 2001](#) used 125 mg/dose. Both trials used intramuscular route of administration. [Cavenee 1993](#) used either one dose of oral amoxicillin (3 g) plus probenecid (1 g) or intramuscular spectinomycin (1 g) as comparison groups. [Ramus 2001](#) used oral cefixime (400 mg) as the control group. Both trials advised sexual abstinence or the use of non-lubricated condoms as co-interventions.

Outcomes

Cure of gonococcal infection (genital, extragenital or both) was the only primary outcome of interest reported by [Cavenee 1993](#) and [Ramus 2001](#). Neither trial reported information related to the incidence of obstetric complications (miscarriage, premature rupture of membranes, preterm delivery, or fetal death), incidence of disseminated gonococcal infections, or the incidence of neonatorum ophthalmia. Both trials reported data on adverse events, in either the mothers or newborns.

Funding sources

Drug companies sponsored the [Cavenee 1993](#) study, but sources of funding were not reported in [Ramus 2001](#).

Declarations of interest (reported by the trialists)

Trial authors did not report any declarations of interest.

See [Characteristics of included studies](#) for details.

Excluded studies

We excluded one study that did not contain enough details in the translation from Chinese to determine if it was a randomised trial, or to understand the group assignments ([Shi 1997](#)).

Risk of bias in included studies

The risk of bias of the included trials is summarised in [Figure 2](#); and [Figure 3](#). Overall, we considered the trials to be at a high risk of bias.

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cavenee 1993
Ramus 2001

Allocation

Random sequence generation

Both trials used random number table for random sequence generation, therefore, we rated them as having low risk of bias for selection bias.

Allocation concealment

Neither trial report information on concealment of sequence generation, therefore, we rated them as having an unclear risk of bias.

Blinding

Blinding of participants and personnel (performance bias)

Both trials were unblinded, therefore, we rated them as having a high risk of performance bias.

Blinding of outcome assessment

Cavenee 1993 did not report information relating to blinding of outcome assessment, therefore, we classified it as being at an unclear risk of detection bias. In contrast, Ramus 2001 reported that "laboratory personnel blinded to the treatment regimen of each study subject" conducted the outcome assessment, and we assessed it as having a low risk of detection bias.

Incomplete outcome data

Cavenee 1993 reported 28% and Ramus 2001 reported 41% withdrawals, and we assessed them both at high risk for attrition bias.

Selective reporting

Both trials reported information about cure and adverse events. The trial authors did not state if they measured other outcomes, and we did not have a study protocol, therefore, we rated this domain as unclear.

Other potential sources of bias

We rated both included trials at high risk of other bias. Both trials presented incomplete data, or used a confusing approach for reporting data, therefore showing bias in the presentation of the data.

Effects of interventions

See: [Summary of findings for the main comparison Intramuscular ceftriaxone compared with oral amoxicillin plus oral probenecid for treating gonorrhoea in pregnancy](#); [Summary of findings 2 Intramuscular ceftriaxone compared with oral cefixime for treating gonorrhoea in pregnancy](#)

Results were based on two trials involving 514 randomised women, only 347 of whom were analysed, due to negative pre-therapy cultures (Cavenee 1993; Ramus 2001). We did not combine study data in a meta-analysis, due to the different medications and comparisons examined.

Primary outcomes (maternal)

Cure of gonococcal infection (genital, extragenital, or both), according to the definition in included trials

Intramuscular ceftriaxone (250 mg) versus oral amoxicillin (3 g) plus oral probenecid (1 g)

Comparison of intramuscular ceftriaxone (250 mg) with oral amoxicillin (3 g) plus oral probenecid (1 g) across one trial showed very low-quality evidence of uncertain differences in the cure of gonococcal infection between groups (risk ratio (RR) 1.07, 95% confidence interval (CI) 0.98 to 1.16; $P = 0.15$; 168 women; [Analysis 1.1](#); [Summary of findings for the main comparison](#); (Cavenee 1993)).

Intramuscular ceftriaxone (125 mg) versus oral cefixime (400 mg)

One trial comparing intramuscular ceftriaxone (125 mg) with oral cefixime (400 mg), found very low-quality evidence of uncertain differences in the cure of gonococcal infection between groups (RR 0.99, 95% CI 0.91 to 1.08; $P = 0.85$; 95 women; [Analysis 2.1](#); [Summary of findings 2](#); (Ramus 2001)).

Incidence of obstetric complications (miscarriage, premature rupture of membranes, preterm delivery, or fetal death)

This outcome was not reported in the included trials.

Incidence of disseminated gonococcal infection

This outcome was not reported in the included trials.

Primary outcome (neonate)

Incidence of neonatorum ophthalmia

This outcome was not reported in the included trials.

Secondary outcomes

Adverse events

Intramuscular ceftriaxone (250 mg) versus oral amoxicillin (3 g) plus oral probenecid (1 g)

Cavenee 1993 reported vomiting after amoxicillin and probenecid in one pregnant woman; RR 0.33, 95% CI 0.01 to 8.07 $P = 0.50$; 168 women; [Analysis 1.2](#); [Summary of findings for the main comparison](#); very low-quality evidence. They also reported pain at the injection site, but did not quantify it. They reported no differences in neonatal malformations (major, minor, or both) between comparison groups.

Intramuscular ceftriaxone (125 mg) versus oral cefixime (400 mg)

Ramus 2001 reported a number of adverse events, but did not quantify them. Women who received intramuscular therapy complained of discomfort at the treatment site, but nothing else.

Neonatal hyperbilirubinaemia was more frequent in neonates whose mothers were exposed to ceftriaxone (compared to the streptomycin group, whose data were not included in this review), but they found no clear differences in neonatal malformations between comparison groups.

DISCUSSION

Summary of main results

This Cochrane Review assessed the clinical effectiveness and harm of antibiotics (different types, routes, or regimens) for treating gonorrhoea in pregnant women, updating and replacing an earlier review on this topic ([Brocklehurst 2002](#)).

We identified two randomised controlled trials that met our inclusion criteria ([Cavenee 1993](#); [Ramus 2001](#)). The experimental groups were intramuscular ceftriaxone 125 mg ([Ramus 2001](#)), or 250 mg ([Cavenee 1993](#)). The comparison groups were oral cefixime (400 mg; ([Ramus 2001](#))), oral amoxicillin (3 g) plus probenecid (1 g; ([Cavenee 1993](#))), and intramuscular spectinomycin (2 g; ([Cavenee 1993](#))). Both trials were conducted in the USA. We rated the risk of bias in both trials as high. We were unable to perform a meta-analysis because the two trials examined different comparison groups. Because spectinomycin is no longer marketed, we did not assess data including that antibiotic ([Higgins 2011](#)).

The main results are as follows.

1. While both trials reported high cure rates with the given antibiotic regimens, there was insufficient evidence to support the use of one regimen over another to achieve a cure.
2. The trials did not report information on obstetrical complications (miscarriage, premature rupture of membranes, preterm delivery, or fetal death), disseminated gonococcal infection, or neonatorum ophthalmia.
3. Overall, we found that the quality of the evidence was very low. See [Summary of findings for the main comparison](#) and [Summary of findings 2](#) for further details.

Overall completeness and applicability of evidence

Both of the included randomised controlled trials failed to detect clear differences between the different antibiotic comparison groups. The small sample sizes in both trials could explain the absence of a difference between the antibiotic regimens in both trials; recognizing that absence of evidence is not evidence of absence ([Altman 1995](#)). One research team conducted both trials, at the same sites. It has been pointed out that single-centre randomised clinical trials overestimate the treatment effect when compared to multicenter randomised clinical trials ([Dechartres 2011](#); [Unverzagt 2013](#)).

Quality of the evidence

The main pitfalls of the evidence found in this Cochrane Review, lie in the small sample sizes, high number of withdrawals, and failure to measure remarkable clinical outcomes in both trials. Therefore, these factors reduce both the internal validity and external validity of both [Cavenee 1993](#) and [Ramus 2001](#). We downgraded the evidence to very low-quality due to high risk of attrition bias, pitfalls in trial design, and imprecision (small sample size and very low number of events).

Both [Cavenee 1993](#) and [Ramus 2001](#) reported insufficient details on randomisation techniques, for either random sequence generation or allocation concealment. Both trials had small sample sizes.

[Nguyen 2017](#) pointed out that simple randomisation did not protect against bias in smaller trials. Thus, it downgraded the quality of the evidence emerging from [Cavenee 1993](#) and [Ramus 2001](#), and reduced its ability to respond to the research question of this Cochrane Review. Thereupon, causal inference from these trials fails ([Backmann 2017](#); [Berger 2008](#)).

Potential biases in the review process

We did an exhaustive search, which included many clinical trial registries, in order to reduce the risk of publication bias ([Figure 1](#)). However, we only identified the same two trials as [Brocklehurst 2002](#), which met our inclusion criteria.

Agreements and disagreements with other studies or reviews

The results of this review are broadly in agreement with those of the earlier review on this topic ([Brocklehurst 2002](#)).

AUTHORS' CONCLUSIONS

Implications for practice

This Cochrane Review found high levels of cure of gonococcal infection in pregnancy with the antibiotic regimens considered. However, there was not enough evidence to support one regimen over another to achieve a cure. This conclusion was based on very low-quality evidence from two trials (involving 514 women), which we assessed to be at a high risk of bias for a number of domains. The harm profiles of the antibiotic regimes featured in this review remain unknown.

Implications for research

The included studies examined single agent antibiotics only. But since 2015, the CDC has recommended dual therapy for gonococcal infections ([CDC 2015](#)). Thus, dual therapy could be studied further in pregnancy, assessing both relative clinical effectiveness and harm, i.e. incidence of obstetric complications (miscarriage, premature rupture of membranes, preterm delivery, fetal death), disseminated gonococcal infection, and neonatorum ophthalmia. Trials could be planned according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; [Chan 2013](#)), and follow CONSORT recommendations ([Turner 2012](#)). Potential trials could also be based on Patient-Centered Outcomes Research Institute (PCORI; ([Frank 2014](#))).

ACKNOWLEDGEMENTS

We want to express our gratitude to Cochrane Pregnancy and Childbirth for improving the quality of this Cochrane Review.

As part of the pre-publication editorial process, this review was commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

The National Institute for Health Research, via Cochrane Infrastructure to Cochrane Pregnancy and Childbirth, supported this project. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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Comunián-Carrasco 2014

Comunián-Carrasco G, Peña-Martí GE, Martí-Carvajal AJ. Antibiotics for gonorrhoea in pregnancy. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: [10.1002/14651858.CD011167](https://doi.org/10.1002/14651858.CD011167)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Cavenee 1993

Methods	Design: parallel (3 arms)
	Country: USA
	Multicenter: yes (2 sites)
	International: no
	Follow-up: 14 days
Participants	Enrolled and randomised: 353
	1. Ceftriaxone: 32.29% (114/353)
	2. Amoxicillin plus probenecid: 34.84% (123/353)
	3. Spectinomycin: 32.86% (116/353)
	Withdrawals: 29% (101/353)
	1. Ceftriaxone: 26.31% (30/114)
	2. Amoxicillin plus probenecid: 32% (39/123)
	3. Spectinomycin: 28% (32/116)
	Reason for exclusion
	1. Negative pre-treatment cultures for <i>N gonorrhoeae</i> : 24.36% (86/353)

Cavenee 1993 (Continued)

2. Lost to follow-up: 4% (15/353)

Analysed: 71.38% (252/353)

1. Ceftriaxone: 73.68% (84/114)
2. Amoxicillin plus probenecid: 68.29% (84/123)
3. Spectinomycin: 72.41% (84/116)

Age (years, mean (standard error or SD not reported))

1. Ceftriaxone: 19.6
2. Amoxicillin plus probenecid: 19.7
3. Spectinomycin: 20.1

Nulliparous

1. Ceftriaxone: 50% (42/84)
2. Amoxicillin plus probenecid: 48% (40/84)
3. Spectinomycin: 51% (43/84)

Ethnicity

1. Ceftriaxone: Black (82%), White (6%), Hispanic (12%)
2. Amoxicillin plus probenecid: Black (84%), White (5%), Hispanic (11%)
3. Spectinomycin: Black (87%), White (6%), Hispanic (7%)

Estimated gestational age (week, mean (standard or error deviation not reported))

1. Ceftriaxone: 23.3
2. Amoxicillin plus probenecid: 21.8
3. Spectinomycin: 21.6

Inclusion criteria

1. Pregnant women with positive gonococcal cultures at any site

Exclusion criteria

1. Allergy to penicillin
2. Declined no inform consent

Interventions	<p>Experimental</p> <ol style="list-style-type: none"> 1. Ceftriaxone: 250 mg intramuscular <p>Control</p> <ol style="list-style-type: none"> 1. Amoxicillin 3 g oral (given 30 minutes after probenecid (1 g orally) 2. Spectinomycin: 2 g intramuscular <p>Cointervention</p> <ol style="list-style-type: none"> 1. Sexual abstinence or non-lubricated condom use
Outcomes	<p>Trial authors did not report outcomes explicitly</p> <p>Likely the outcomes were:</p> <ol style="list-style-type: none"> 1. Cure 2. Safety 3. Concomitance of rectal and pharyngeal gonorrhoea in either urban or indigent pregnant women.

Cavenee 1993 (Continued)

Notes

Identifier trial number: not supplied

Sample size estimation a priori: yes

Trial date: January 1990 to March 1992

Trial sponsor: Roche Laboratories, The Upjohn Company, and Wyeth-Ayerst Laboratories

Role of sponsor: not reported

Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "...via a random number table..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote "...to one of three unblinded treatment..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall withdrawals: 28% (101/353). By arm: 1. Ceftriaxone: 26.31% (30/114) 2. Amoxicillin plus probenecid: 34.21% (39/114) 3. Spectinomycin: 27.58% (32/116)
Selective reporting (reporting bias)	Unclear risk	Trial authors did not state if they measured other outcomes, and we did not have a study protocol. They reported information regarding cure and adverse events.
Other bias	High risk	Bias in the presentation of the data. Trial had incomplete data or used an approach some confuse for reporting data.

Ramus 2001

Methods

Design: parallel (2 arms)

Country: USA

Multicenter: yes

International: no

Ramus 2001 (Continued)

Follow-up: up to 14 days

Participants	<p>Enrolled: 161</p> <p>Randomised: 161</p> <ol style="list-style-type: none"> 1. Ceftriaxone: unknown 2. Cefixime: unknown <p>Withdrawal: 41% (66/161)</p> <p>Analysed: 95</p> <ol style="list-style-type: none"> 1. Ceftriaxone: 43 2. Cefixime: 52 <p>Age (year, mean (SD))</p> <ol style="list-style-type: none"> 1. Ceftriaxone: 18.9 (2.7) 2. Cefixime: 19.3 (3.9) <p>Gestational age at treatment (week, mean (SD))</p> <ol style="list-style-type: none"> 1. Ceftriaxone: 21.3 (8.1) 2. Cefixime: 20.8 (9.7) <p>Overall (N = 95)</p> <ol style="list-style-type: none"> 1. Endocervical infection: 91% (86/95) 2. Anal infection: 41% (39/95) 3. Pharyngeal infection: 12% (11/95) 4. Concomitant endocervical chlamydial infection: 53 (50/95) <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Allergy to penicillin or any cephalosporin
Interventions	<p>Trial authors did not discriminate between experimental and control groups. Information on manufacturers was unknown.</p> <ol style="list-style-type: none"> 1. Ceftriaxone 125 mg intramuscularly 2. Cefixime 400 mg orally <p>Cointervention: sexual abstinence or non lubricated condom use</p>
Outcomes	<p>Efficacy measured using cure cultures.</p> <p>Trial authors did not discriminate outcomes as primary or secondary.</p>
Notes	<p>Identifier trial number: not supplied</p> <p>Sample size estimation a priori: yes</p> <p>Trial date: April 1994 to October 1997</p> <p>This trial was stopped early in 1997 for decreasing frequency of gonorrhoea in the patient population, which limited the ability to achieved the estimated sample size.</p> <p>Sponsor trial: not supplied</p> <p>Role of sponsor: not supplied</p> <p>Conflict of interest: not declared</p>

Ramus 2001 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "...use of a random number table..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote "...which were unblinded..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "...laboratory personnel blinded to the treatment regimen of each study subject..."
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Withdrawal: 41% (66/161)</p> <p>Reasons:</p> <ol style="list-style-type: none"> 1. Negative pre treatment cultures for <i>N gonorrhoeae</i>: 51 2. Lost to follow-up or had follow-up after 14 days after therapy: 15
Selective reporting (reporting bias)	Unclear risk	Trial authors did not state if they measured other outcomes, and we did not have a study protocol. They reported information regarding cure and adverse events.
Other bias	High risk	<p>Bias in the presentation of the data</p> <p>Trial had incomplete data or used an approach some confuse for reporting data.</p>

SD: standard deviation

N gonorrhoeae: *Neisseria gonorrhoeae*

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Shi 1997	Translation of the Chinese report was unclear if this was a randomised trial, how group allocation was done, or which group was considered the control and the treatment groups. Thus, it was impossible to include the trial in any meaningful way.

DATA AND ANALYSES

Comparison 1. Intramuscular ceftriaxone (250 mg) versus oral amoxicillin (3 g) plus oral probenecid (1 g)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure of gonococcal infection	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.16]
2 Adverse events	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.07]

Analysis 1.1. Comparison 1 Intramuscular ceftriaxone (250 mg) versus oral amoxicillin (3 g) plus oral probenecid (1 g), Outcome 1 Cure of gonococcal infection.

Analysis 1.2. Comparison 1 Intramuscular ceftriaxone (250 mg) versus oral amoxicillin (3 g) plus oral probenecid (1 g), Outcome 2 Adverse events.

Comparison 2. Intramuscular ceftriaxone (125 mg) versus oral cefixime (400 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure of gonococcal infection	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.08]

Analysis 2.1. Comparison 2 Intramuscular ceftriaxone (125 mg) versus oral cefixime (400 mg), Outcome 1 Cure of gonococcal infection.

APPENDICES

Appendix 1. Medical glossary

Term	Definition	Source
Disseminated gonococcal infection	Disseminated gonococcal infection results from bacteraemic spread of the sexually transmitted pathogen, <i>Neisseria gonorrhoeae</i> , which can lead to a variety of clinical symptoms and signs, such as tenosynovitis, dermatitis, and multiple skin lesions.	www.uptodate.com/contents/dis-seminated-gonococ-cal-infection
Fetal death	Death of the developing young in utero. Birth of a dead fetus is stillbirth.	US National Library of Medicine
Fetal membranes, premature rupture	Spontaneous tearing of the membranes surrounding the fetus any time before the onset of obstetric labour. Preterm premature rupture of membrane is membrane rupture before 37 weeks of gestation.	US National Library of Medicine
Fitz-Hugh-Curtis syndrome or gonococcal perihepatitis	Peritonitis and hepatitis associated with pelvic inflammatory disease caused by Chlamydia Trachomatis or Neisseria Gonorrhoeae infections. The diaphragm may also be affected.	US National Library of Medicine
Low birthweight	An infant having a birthweight of 2500 g (5.5 lb) or less, very low birthweight refers to infants having a birthweight of 1500 g (3.3 lb) or less.	US National Library of Medicine
Miscarriage or abortion, spontaneous	Expulsion of the product of fertilisation before completing the term of gestation and without deliberate interference.	US National Library of Medicine
Ophthalmia neonatorum	Acute conjunctival inflammation in the newborn, usually caused by maternal gonococcal infection. The causative agent is <i>Neisseria gonorrhoeae</i> . The baby's eyes are contaminated during passage through the birth canal.	US National Library of Medicine
Pelvic inflammatory disease	A spectrum of inflammation involving the female upper genital tract and the supporting tissues. It is usually caused by an ascending infection of organisms from the endocervix. Infection may be confined to the uterus (endometritis), the fallopian tubes; (salpingitis); the ovaries (oophoritis), the supporting liga-	US National Library of Medicine

(Continued)

ments (parametritis), or may involve several of the above uterine appendages. Such inflammation can lead to functional impairment and infertility.

Preterm delivery or pre-mature birth

Childbirth before 37 weeks of pregnancy (259 days from the first day of the mother's last menstrual period, or 245 days after fertilisation).

[US National Library of Medicine](#)

Appendix 2. LILACS search strategy (5 April 2017)

gonorrhea AND pregnancy
Results: 23 hits (0 trials)

Appendix 3. WHO International Clinical Trials. Registry Platform (5 April 2017)

gonorrhea AND pregnancy
Results: 0 hits

Appendix 4. ISRCTN registry (5 April 2017)

gonorrhoea AND pregnancy
Results: 2 hits (0 trials)

Appendix 5. ClinicalTrials.gov search strategy (5 April 2017)

gonorrhea AND pregnancy (0 trials)
Results: 20 hits

Appendix 6. Epistemonikos search strategy (5 April 2017)

gonorrhea AND pregnancy
Results: 14 hits (2 trials)

CONTRIBUTIONS OF AUTHORS

Gabriella Comunián-Carras is the guarantor for the review. All three review authors assessed trials for inclusion, trial quality and performed data extraction. Gabriella Comunián-Carrasco drafted the review. Guiomar E Peña-Martí and Arturo Martí-Carvajal revised the review.

DECLARATIONS OF INTEREST

Gabriella Comunián-Carrasco - none known.

Guiomar E Peña-Martí - none known.

Arturo Martí-Carvajal - none known.

SOURCES OF SUPPORT

Internal sources

- Universidad de Carabobo, Venezuela.

External sources

- Iberoamerican Cochrane Network, Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are differences between the protocol for this review ([Comunián-Carrasco 2014](#)), and the full review - these are listed below:

- We searched in the LILACS database, which reduced the risk of publication bias.
- We edited the review title to make it clear that the review was about treating gonorrhoea.
- We edited some methods sections in line with the current standard methods of Cochrane Pregnancy and Childbirth.
- We removed 'failure to eradicate gonorrhoea in mother treated', since it was the inverse of the main outcome.
- We reported adverse events related to either mother or newborn.

- We did not conduct trial sequential analysis (TSA) because we did not conduct a meta-analysis and also because of the high incidence of 'cure of gonococcal infection' in both trials for each of the comparison groups. Although these results could be considered to be false negatives, due to small sample sizes, what is really useful is how clinically relevant these results are. The high levels of cured gonorrhoea in pregnancy reduces the chance of conducting new RCTs in this field. We believe that not conducting the TSA, as planned in our protocol, in no way impairs the information presented in this Cochrane review in relation to the clinical effectiveness and any adverse effects of using antibiotic regimens for treating gonorrhoea in pregnancy.

INDEX TERMS

Medical Subject Headings (MeSH)

Amoxicillin [administration & dosage] [therapeutic use]; Anti-Bacterial Agents [administration & dosage] [*therapeutic use]; Cefixime [administration & dosage] [therapeutic use]; Ceftriaxone [administration & dosage] [therapeutic use]; Gonorrhea [*drug therapy]; Pregnancy Complications, Infectious [*drug therapy]; Probenecid [administration & dosage] [therapeutic use]; Randomized Controlled Trials as Topic; Spectinomycin [administration & dosage] [therapeutic use]

MeSH check words

Female; Humans; Pregnancy