Antibiotics for gonorrhoea in pregnancy (Review)

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ABSTRACT

Background
Neisseria 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 infection. It can also cause endometritis and pelvic sepsis in the mother.

Objectives
The objective of this review was to assess the effects of antibiotic regimens in the treatment of genital infection with gonorrhoea during pregnancy with respect to neonatal and maternal morbidity.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 January 2007).

Selection criteria
Randomized trials of one regimen of antibiotic versus another in pregnant women with culture confirmed genital gonococcal infection.

Data collection and analysis
Eligibility and trial quality were assessed by one review author.

Main results
Two trials involving 346 women were included. The only outcome included in these trials was the incidence of 'cure' assessed by bacterial culture. Failure to achieve 'microbiological cure' was similar for each antibiotic regimen: amoxicillin plus probenecid compared with spectinomycin (Peto odds ratio (Peto OR) 2.29, 95% confidence interval (CI) 0.74 to 7.08), amoxicillin plus probenecid compared with ceftriaxone (Peto OR 2.29, 95% CI 0.74 to 7.08) and ceftriaxone compared with cefixime (Peto OR 1.22, 95% CI 0.16 to 9.01). Side-effects were uncommon for all the tested regimens.

Authors' conclusions
The number of women included in each of the comparisons is small and therefore, although no differences were detected between the different antibiotic regimens, the trials were limited in their ability to detect important but modest differences. For women who are allergic to penicillin, this review provides some reassurance that treatment with ceftriaxone or spectinomycin appears to have similar effectiveness in producing microbiological cure.

PLAIN LANGUAGE SUMMARY

Pregnant women with gonorrhoea who take penicillin, spectinomycin or ceftriaxone are much less likely to show signs of infection

Neisseria gonorrhoeae is a bacteria transmitted (passed) during sex, causing an infection in the genital area. Pregnant women with gonorrhoea may pass the infection to babies during birth. This can affect the baby's eyesight, causing blindness. The review of trials found evidence that pregnant women who take penicillin, spectinomycin, ceftriaxone or cefixime are much less likely to have signs of gonorrhoea a week to 10 days later. Further research is needed to find out which antibiotic treatment is the best for preventing infection of the baby.

BACKGROUND

Neisseria gonorrhoea causes a sexually transmitted infection which, although uncommon in developed countries, is a major public health issue in many developing countries (Edwards 1978; Laga 1986). Gonorrhoea in pregnancy has been associated with prelabour rupture of the membranes and preterm delivery, although this relationship may be casual rather than causal (Amstey 1976).

Neisseria gonorrhoeae can be transmitted from the mother's genital tract to the neonate at the time of delivery and occasionally, when there is prolonged rupture of the membranes, it can be transmitted to the fetus before birth. The usual manifestation of neonatal infection is gonococcal ophthalmia neonatorum. The risk of transmission from an infected mother is between 30% and 47% (Fransen 1986; Galega 1984). Gonococcal ophthalmia neonatorum begins in the first few days of life, is manifest by a profuse purulent conjunctival discharge and is frequently bilateral. If left untreated, this infection will eventually lead to blindness although the risk of blindness has not been accurately quantified. Occasionally the neonate may develop gonococcal infection elsewhere such as gonococcal arthritis.

In the postpartum period gonorrhoea can cause endometritis and pelvic sepsis in the mother, which may be severe.

Gonorrhoea was one of the first infections to be treated with penicillin in the 1940s and there have been no randomized controlled trials of the effectiveness of penicillin for people with symptomatic gonorrhoea. Penicillin continues to be used for the treatment of gonorrhoea in pregnancy in most countries which have a low incidence of penicillinase-producing Neisseria gonorrhoeae (PPNG). However, for women who are sensitive to penicillin or who are infected with PPNG, there is uncertainty as to what is the most effective antibiotic therapy.

OBJECTIVES

To determine what antibiotic regimens are effective in the treatment of genital infection with gonorrhoea in pregnancy. Any antibiotic will be compared with penicillin. If there are sufficient trials, these will be stratified into groups of similar antibiotics compared with penicillin. In addition, any trials of alternative antibiotics comparisons will be included to determine their relative effectiveness, or at least suggest which comparisons may be useful to investigate in future trials.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials comparing either (i) penicillin with another antibiotic or (ii) two or more other alternative antibiotics in pregnant women with genital gonococcal infection (defined as culture of Neisseria gonorrhoea from the genital tract). Historical control studies are not included.

Types of participants

Women of any age, at any stage of pregnancy with a diagnosis of genital gonococcal infection (symptomatic or asymptomatic). Co-infection with other sexually transmitted infection is not a reason to exclude women from the review.

Types of intervention

Penicillin (any dosage regimen, any agent, any route of administration) compared with any other antibiotic agent (any dosage regimen, any agent, any route of administration). Similarly, comparisons of any two or more antibiotic regimens.

Types of outcome measures

The clinically meaningful outcomes selected for this review are:

(i) incidence of neonatal ophthalmia neonatorum;
(ii) incidence of neonatal gonococcal infection other than ophthalmia neonatorum;
(iii) incidence of postpartum sepsis in the treated mothers;
(iv) failure to eradicate gonorrhoea from the genital tract of treated mothers as determined by gonococcal culture after treatment (failure to achieve 'microbiological cure');
(v) side-effects sufficient to stop or change treatment;
(vi) side-effects not sufficient to stop or change treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 January 2007).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 36 journals plus BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We did not apply any language restrictions.

METHODS OF THE REVIEW

All potential trials are selected for eligibility according to the criteria specified in the protocol. The information necessary for the review is abstracted from the published trial reports. No additional information was requested from the authors.

All trials were assessed for methodological quality using standard Cochrane criteria. Summary odds ratios have been calculated if appropriate (i.e. there is no evidence of significant heterogeneity) using the Cochrane statistical software (RevMan 2000).

DESCRIPTION OF STUDIES

See 'Characteristics of included studies'.

METHODOLOGICAL QUALITY

Cavenee 1993
The trial by Cavenee et al included three treatment arms and the allocation of treatment was reported as being randomized. The exact process used for randomization was not specified.

Three-hundred and fifty-three women referred to a specialist clinic because of a previous positive culture for gonorrhoea were randomized. Of these, only 267 had the cultures confirmed at the time of randomization. The remaining 86 women (24%) were excluded from the analysis. This is not, therefore, an intention-to-treat analysis.

Treatment was not blinded, although the outcome of 'microbiological cure' is unlikely to be greatly affected by the knowledge of the allocated treatment. Women were excluded from the analysis (a) if they did not return to the clinic within 14 days of receiving treatment for a test of cure ('microbiological cure') and (b) if they admitted to having had unprotected intercourse with an untreated partner since starting the trial treatment. This amounted to 15 women out of the 267 women who were randomized (6%).

Ramus 2001
The trial by Ramus et al, initially reported in abstract in 1996, stated that randomization had been used. The exact process used for randomization is not specified.

One-hundred and sixty-one women referred to a specialist clinic because of a positive culture for gonorrhoea were randomized. Of these, only 95 had the cultures confirmed at the time of randomization. The remaining 51 (32%) were excluded from the analysis. This is not, therefore, an intention-to-treat analysis.

Treatment was not blinded, although the outcome of 'microbiological cure' is unlikely to be greatly affected by the knowledge of the allocated treatment. Women were excluded from the analysis if they did not return to the clinic within 14 days of receiving treatment for a test of cure ('microbiological cure'). This amounted to 15 women out of the 161 women who were randomized (9%).

RESULTS

Two trials involving 346 women were included. All the tested antibiotic regimens demonstrated a high level of effectiveness as judged by 'microbiological cure', with eradication rates of between 89% and 97%. Failure to achieve 'microbiological cure' was similar for each antibiotic regimen: amoxicillin plus probenecid compared with spectinomycin (Peto odds ratio (Peto OR) 2.29, 95% confidence interval (CI) 0.74 to 7.08), amoxicillin plus probenecid compared with ceftriaxone (Peto OR 2.29, 95% CI 0.74 to 7.08) and ceftriaxone compared with cefixime (Peto OR 1.22, 95% CI 0.16 to 9.01). There is no convincing evidence that any one of the tested antibiotic regimens is superior to the treatments with which they were compared. The number of women included in each of the comparisons is small and therefore, although no differences were detected between the different antibiotic regimens, the trials were limited in their ability to detect important but modest differences.

There appear to be few side-effects associated with any of the tested regimens. No women in the trial by Ramus 2001 reported any side-effects sufficient to stop treatment and the trial by Cavenee 1993 reported that only one woman in the whole trial reported vomiting after treatment.

DISCUSSION

The aim of treating gonorrhoea during pregnancy is to eradicate the infection and therefore prevent the consequences of that infection. These consequences will include neonatal infection, postpartum sepsis for the mother and the consequences of transmission to sexual partners. 'Microbiological cure' is used in these trials as an alternative measure of eradication of infection, the assumption being that 'microbiological cure' equals eradication and no subsequent neonatal or maternal disease. This assumption may not

be true, however, and the extent to which it is not true may vary between the different antibiotics being compared. Thus, if both agents appear to be equally effective in terms of their effect on 'microbiological cure', there may still be differences in their effect on more substantive outcome measures such as ophthalmia neonatorum. Neither trial reported any substantive outcome measures.

The concept that genital cultures may not accurately reflect whether a woman is or is not infected with gonorrhoea is supported by findings from both of the trials (Cavenee 1993; Ramus 2001). In these trials, women were referred to a specialist clinic because they had culture evidence of genital gonococcal infection. These women then had repeat cultures taken and only 68% to 76% of the original group had evidence of gonorrhoea on a second sample. This may reflect spontaneous cure or it may reflect the inaccuracy of genital cultures as a method of detecting women who are infected. Either way, it is possible that evidence of 'microbiological cure' may be a less reliable outcome measure than has been assumed and evidence that there were no or few episodes of disease in the neonates or the mothers postnatally would have been more reassuring.

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests that any of the antibiotic regimens tested in these trials may be suitable for the treatment of gonorrhoea in pregnancy in terms of their effect on 'microbiological cure'. There is a suggestion that amoxicillin with probenecid may be a little less effective than spectinomycin or ceftriaxone although the numbers in the trials are too small to state this with confidence.

For women who are allergic to penicillin this review provides reassurance that treatment with ceftriaxone or spectinomycin is at least as equally effective in producing 'microbiological cure'. The two trials did not include populations with a high prevalence of penicillinase-producing Neisseria gonorrhoeae strains and little can be concluded about the relative effectiveness of these antibiotic regimens in such populations.

When comparing two non-penicillin antibiotics, the only direct comparison which has been made is a comparison between ceftriaxone and cefixime. This suggested little difference in terms of their effectiveness but once again the numbers involved are small. A conclusive demonstration that the two drugs are equally effective would be of interest in that one is given orally and one by intramuscular injection.

Implications for research

Any further trials of antibiotic treatment for gonorrhoea in pregnancy should include more substantive outcome measures.

Similarly, information about side-effects should be collected and clearly presented, particularly when assessing the relative merits of two different antibiotics. If the drugs seem to be equally effective, there may be differences in their side-effect profile which would favour the adoption of one drug over the other and, without this information, the clinician is left uncertain about which policy to adopt.

Finally, the association between genital gonococcal infection and adverse perinatal outcome in terms of prelabour rupture of the membranes and preterm delivery merits further investigation. The evidence to date is entirely observational and the assumption that early detection and treatment of gonorrhoea in pregnancy will alter subsequent perinatal outcome requires testing in randomized controlled trials.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

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SOURCES OF SUPPORT

External sources of support

- Department of Health UK

Internal sources of support

- No sources of support supplied

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Cavenee 1993 *{published data only}*

Cavenee M, Farris R, Rawlins S, Mayfield J, Wendel G. Treatment of gonorrhea in pregnancy (abstract 194). *American Journal of Obstetrics and Gynecology* 1991;**164**:300.

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Ramus 2001 *{published data only}*

Ramus R, Mayfield J, Wendel G. Evaluation of the current CDC recommended treatment guidelines for gonorrhea in pregnancy (abstract 358). *American Journal of Obstetrics and Gynecology* 1996; **174**:409.

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Amstey 1976

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Fransen 1986

Fransen L, Nsaze H, Klauss V, Van-der-Stuyft P, D'Costa L, Brunham RC, et al. Ophthalmia neonatorum in Nairobi, Kenya, the role of Neisseria gonorrhoea and Chlamydia trachomatis. *Journal of Infectious Diseases* 1986;**153**:862–9.

Galega 1984

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Laga 1986

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RevMan 2000

The Cochrane Collaboration. Review Manager (RevMan). 4.1 for Windows. Oxford, England: The Cochrane Collaboration, 2000.

References to other published versions of this review

Brocklehurst 2002

Brocklehurst P. Gonorrhoea in pregnancy (Cochrane Review). *The Cochrane Library* 2002, Issue 1.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Cavenee 1993
Methods	'Random-number table'.
Participants	352 women referred with a positive gonorrhoea culture in pregnancy.
Interventions	Ceftriaxone 250 mg IM or amoxicillin 3 g PO given 30 minutes after probenecid 1 g PO or spectinomycin 2 g IM.
Outcomes	Test of cure - performed 1 week after treatment. No neonatal outcomes or postpartum outcomes described. Side-effects inadequately reported.
Notes	Not blinded. 86 women were excluded from the analysis because the immediate pre-treatment cultures did not confirm the diagnosis. Another 15 were lost to follow up. 102 women (40%) had concomitant endocervical chlamydia trachomatis infection.

Allocation concealment	A – Adequate

Study	**Ramus 2001**
Methods	'Random-number table'.
Participants	161 women referred with a positive gonorrhoea culture in pregnancy.
Interventions	Ceftriaxone 125 mg IM or cefixime 400 mg PO.
Outcomes	Test of cure 4-10 days after treatment.
Notes	Not blinded. 51 women were excluded from the analysis because the immediate pre-treatment cultures did not confirm the diagnosis. Another 15 were lost to follow up. 50 women (53%) had concomitant endocervical chlamydia trachomatis infection.
Allocation concealment	A – Adequate

IM: intramuscular
PO: orally

ANALYSES

Comparison 01. Any penicillin versus any other antibiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure to achieve microbiological cure	1	248	Peto Odds Ratio 95% CI	2.49 [0.88, 7.02]

Comparison 02. Amoxicillin and probenicid versus spectinomycin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure to achieve microbiological cure	1	168	Peto Odds Ratio 95% CI	2.29 [0.74, 7.08]

Comparison 03. Amoxicillin and probenicid versus ceftriaxone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure to achieve microbiological cure	1	168	Peto Odds Ratio 95% CI	2.29 [0.74, 7.08]

Comparison 04. Ceftriaxone versus cefixime

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure to achieve microbiological cure	1	95	Peto Odds Ratio 95% CI	1.22 [0.16, 9.01]
02 Side-effects sufficient to stop treatment	1	95	Peto Odds Ratio 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Disease Transmission, Vertical [*prevention & control]; Gonorrhea [*drug therapy; *transmission]; Infant, Newborn; Pregnancy Complications, Infectious [*drug therapy]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Antibiotics for gonorrhoea in pregnancy
Authors	Brocklehurst P
Contribution of author(s)	Information not supplied by author
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GRAPHS AND OTHER TABLES

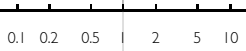
Analysis 01.01. Comparison 01 Any penicillin versus any other antibiotic, Outcome 01 Failure to achieve microbiological cure

Review: Antibiotics for gonorrhoea in pregnancy

Comparison: 01 Any penicillin versus any other antibiotic

Outcome: 01 Failure to achieve microbiological cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Cavenee 1993	9/84	8/164		100.0	2.49 [0.88, 7.02]
Total (95% CI)	84	164		100.0	2.49 [0.88, 7.02]
Total events: 9 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.72 p=0.09					



Analysis 02.01. Comparison 02 Amoxicillin and probenicid versus spectinomycin, Outcome 01 Failure to achieve microbiological cure

Review: Antibiotics for gonorrhoea in pregnancy

Comparison: 02 Amoxicillin and probenicid versus spectinomycin

Outcome: 01 Failure to achieve microbiological cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Cavenee 1993	9/84	4/84		100.0	2.29 [0.74, 7.08]
Total (95% CI)	84	84		100.0	2.29 [0.74, 7.08]
Total events: 9 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.44 p=0.2					

Analysis 03.01. Comparison 03 Amoxicillin and probenicid versus ceftriaxone, Outcome 01 Failure to achieve microbiological cure

Review: Antibiotics for gonorrhoea in pregnancy

Comparison: 03 Amoxicillin and probenicid versus ceftriaxone

Outcome: 01 Failure to achieve microbiological cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Cavenee 1993	9/84	4/84		100.0	2.29 [0.74, 7.08]
Total (95% CI)	84	84		100.0	2.29 [0.74, 7.08]
Total events: 9 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.44 p=0.2					

Analysis 04.01. Comparison 04 Ceftriaxone versus cefixime, Outcome 01 Failure to achieve microbiological cure

Review: Antibiotics for gonorrhoea in pregnancy

Comparison: 04 Ceftriaxone versus cefixime

Outcome: 01 Failure to achieve microbiological cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ramus 2001	2/43	2/52		100.0	1.22 [0.16, 9.01]
Total (95% CI)	43	52		100.0	1.22 [0.16, 9.01]
Total events: 2 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.19 p=0.8					

Analysis 04.02. Comparison 04 Ceftriaxone versus cefixime, Outcome 02 Side-effects sufficient to stop treatment

Review: Antibiotics for gonorrhoea in pregnancy

Comparison: 04 Ceftriaxone versus cefixime

Outcome: 02 Side-effects sufficient to stop treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Ramus 2001	0/43	0/52		0.0	Not estimable
Total (95% CI)	43	52		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable