Interventions for trichomoniasis in pregnancy (Review)

Gülmezoglu AM

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ABSTRACT

Background
Vaginitis due to Trichomonas vaginalis is one of the most common of sexually transmitted diseases. Trichomoniasis affects women during pregnancy as well but it is not clearly established whether it causes preterm birth and other pregnancy complications.

Objectives
The objective of this review was to assess the effects of various treatments for trichomoniasis during pregnancy.

Search strategy
The Cochrane Pregnancy and Childbirth Group trials register was searched (15 January 2004).

Selection criteria
Randomized trials comparing antitrichomonas agents during pregnancy. Trials including symptomatic or asymptomatic women with trichomoniasis were eligible.

Data collection and analysis
Eligibility and trial quality was assessed by one reviewer.

Main results
Two trials with 842 pregnant women were included. In both trials around 90% of women were cleared of trichomonas in the vagina after treatment. In the US trial women with asymptomatic trichomoniasis between 16 to 23 weeks were treated with metronidazole on two occasions at least two weeks apart. The trial was stopped before reaching its target recruitment because metronidazole was not effective in reducing preterm birth and there was a likelihood of harm (relative risk: 1.8; 95% confidence interval: 1.2 to 2.7). The South African trial recruited women later in pregnancy and did not have the design and power to address adverse clinical outcomes.

Authors' conclusions
Metronidazole, given as a single dose, is likely to provide parasitological cure for trichomoniasis, but it is not known whether this treatment will have any effect on pregnancy outcomes. The cure rate could probably be higher if more partners used the treatment.

PLAIN LANGUAGE SUMMARY

Metronidazole is effective against a trichomoniasis infection during pregnancy, but may increase the risk of preterm and low birthweight babies

Trichomoniasis is a very common sexually transmitted infection. Symptoms include vaginal itching and discharge. It is not clear if pregnant women with trichomoniasis are more likely to give birth preterm, or have other pregnancy complications. The review of trials found that the drug metronidazole is effective against trichomoniasis when taken by women and their partners during pregnancy, but it may harm the baby. Of the two clinical trials reviewed, one was stopped early because women taking metronidazole were more likely to give birth preterm and have low-birthweight babies. Further research into trichomoniasis treatments for pregnant women is needed.

BACKGROUND

Vaginitis due to Trichomonas vaginalis is one of the most common of sexually transmitted diseases. The World Health Organization (WHO) estimates that around 120 million women suffer from trichomoniasis every year (WHO 1994). Infection is characterised by green-yellow frothy vaginal discharge, dyspareunia, irritation of the vulva and urethra causing vulvovaginal soreness, itching and dysuria. The diagnosis is usually made on clinical findings and identification of the parasite in wetmount smear. Wetmount smear is a cheap and quick method whereby motile protozoa are identified under the light microscope. More sensitive techniques such as culture, immunofluorescence and enzyme immunoassay are also available although they are more costly, time consuming and therefore not used very often in busy clinics, especially in developing countries (Lossick 1991).

It is not clear whether Trichomonas vaginalis infection during pregnancy has any effect on adverse pregnancy outcomes. Concern has been raised about the possibility of increasing the transmission of HIV infection because of impairment of the vaginal mucosal barrier. It may, however, be difficult to single out any microorganism with regard to these adverse effects as many types of vaginitis are polymicrobial.

Metronidazole has been the main agent used in the treatment of trichomoniasis since the 1960s. It is generally advised to withhold metronidazole treatment during pregnancy until after the first trimester (Lossick 1991; Murphy 1994). In early pregnancy other agents such as clotrimazole have been recommended as a local application. Tinidazole, ornidazole and nimorazole are other nitroimidazoles which are also effective against trichomonas. The Cochrane review comparing the effectiveness of various treatment options for trichomoniasis in nonpregnant women found metronidazole and other nitroimidazole group drugs effective in treating the infection (Forna 2002). There were no major differences between different nitroimidazoles.

Trichomoniasis during pregnancy is a common occurrence in both developing and developed countries, treated by various health care professionals. The possible effects of trichomoniasis on pregnancy, the effectiveness of different preparations and different routes are potential areas of controversy. It is therefore important to document the evidence from randomized trials regarding the effectiveness and safety of various treatment protocols.

OBJECTIVES

To determine the effectiveness of various drug treatments for trichomoniasis in pregnant women.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Any randomized trial in which an attempt is made to compare different forms of treatment for trichomoniasis during pregnancy.

Types of participants

Pregnant women with:

1. Trichomoniasis diagnosed by either wetmount smear or any other laboratory test in addition to clinical findings (symptomatic women).
2. Asymptomatic women with a laboratory diagnosis of trichomoniasis.

Types of intervention

Any treatment versus no treatment.
Comparison of two different agents.
Comparison of different doses of the same agent.
Systemic versus local treatment.
Single dose (including one day) versus longer (five to 10 day) treatment.

Types of outcome measures

Adverse pregnancy outcomes such as preterm birth, low birthweight and intrauterine infection.
Parasitological cure confirmed by repeat testing after treatment.
Symptomatic relief (clearance of discharge, soreness, itching).
Side effects and complications of treatment.
Recurrence of infection.
Satisfaction with treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

This review has drawn on the search strategy developed for the Pregnancy and Childbirth Group as a whole. The full list of journals and conference proceedings as well as the search strategies for the electronic databases, which are searched by the Group on behalf of its reviewers, are described in detail in the 'Search strategies for the identification of studies section' within the editorial information about the Cochrane Pregnancy and Childbirth Group. Briefly, the Group searches on a regular basis MEDLINE, the Cochrane Controlled Trials Register and reviews the Contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service.

Relevant trials, which are identified through the Group's search strategy, are entered into the Group's specialised Register of Controlled Trials. Please see Review Group's details for more detailed information. Date of last search: 15 January 2004.

METHODS OF THE REVIEW

Trials under consideration were evaluated for methodological quality and appropriateness for inclusion, without consideration of their results.

Methodological quality was assessed in terms of adequacy of allocation concealment as described in Clarke 2000.

Included trial data were processed as described in Clarke 2000.

DESCRIPTION OF STUDIES

Two trials were included that differed in several ways. Ross 1983 trial was conducted in South Africa and included both asymptomatic and symptomatic women whereas Klebanoff 2001 included only asymptomatic women attending antenatal clinics in 15 centres across the USA. The diagnosis was made by wetmount smear in the South African trial and by culture in the US trial. The US trial was set to investigate whether treatment of asymptomatic trichomoniasis could prevent preterm birth and the enrolment took place between 16 to 23 weeks whereas in the South African trial enrolment was much later in pregnancy. The dose of metronidazole used in the US trial was double (2g 48 hours apart) the dose used in the South African trial and was repeated after two weeks.

In the South African trial, 225 out of the 376 (60%) antenatal women tested were positive. In the US trial only 7.6% (2377/31157) of women were trichomonas positive.

Metronidazole was given to women for their partners to take in both studies.

METHODOLOGICAL QUALITY

The allocation was by alternation in the Ross 1983 trial which is prone to selection bias. The Klebanoff 2001 trial was double-blind with the use of identical placebos. The randomization schedule was generated by computer. However, no information is given regarding the allocation concealment and actual manner with which allocation was made.

In the South African trial the comparison of persistence of infection is made between the 'one month' follow-up results in the treatment group and 'persistence of infection until delivery' in the control group.

RESULTS

Both studies showed high rates of parasitological cure (around 90%) following treatment. The risks of preterm birth (relative risk (RR): 1.8; 95% confidence interval (CI): 1.2 to 2.7) and low birth weight (RR: 1.4; 95% CI: 0.9 to 2.1) were increased in the metronidazole group in the US study (Klebanoff 2001).

In the South African trial (Ross 1983) there were no differences in mean birth weight, gestational age and the incidence of low birth weight (12% in treated versus 11% in control) between the two groups.

DISCUSSION

Trichomoniasis is a troublesome infection which causes significant discomfort and is associated with adverse pregnancy outcomes (Cotch 1997; French 1999). Both trials included in the review show reasonable rates of parasitological cure and this could probably be improved if more emphasis is put on partner treatment. Despite the association of Trichomonas vaginalis with preterm birth and low birth weight, the US trial results suggest that a protective effect on preterm birth and low birth weight is unlikely. Surprisingly, there was an increase in preterm births in women receiving metronidazole. The trial was stopped because it was highly unlikely that the treatment would be effective if all women would have been recruited. However, the question of whether the drug actually increases the preterm birth rate remains unanswered. Recruitment was stopped after 617 women were randomized (32% of total planned sample size). The authors discuss the possible reasons for an increase in preterm birth rate including the possibility of toxic substances being released from destroyed Trichomonas and an unpredicted change in the vaginal flora triggered by the high dose metronidazole treatment. Whether inclusion of symptomatic women would have changed the result is unknown. The literature on metronidazole treatment during pregnancy and preterm birth is not conclusive. Hauth et al (Hauth 1995) used metronidazole and erythromycin and Morales et al (Morales 1994) used metronidazole alone in women with bacterial vaginosis (BV) and high-risk of preterm birth and in both studies preterm birth rates were reduced. McDonald et al (McDonald 1997) on the other hand did not find a clinically or statistically significant difference in preterm birth rate with metronidazole in women with bacterial vaginosis. With the limited evidence currently available, metronidazole treatment of asymptomatic trichomoniasis infection does not seem to reduce preterm birth.

AUTHORS' CONCLUSIONS

Implications for practice

This review found no evidence to support the use of metronidazole in pregnant asymptomatic women with trichomonas vaginalis. It is not clear why metronidazole should cause adverse pregnancy outcomes when it is effective in clearing the infection. Given that Trichomonas vaginalis is a sexually transmitted infection with unpleasant symptoms and associated with adverse outcomes includ-

ing facilitating HIV transmission (Sorvillo 2001), it would seem prudent to treat symptomatic women during pregnancy.

Implications for research

Metronidazole, or nitro-imidazoles in general, are the first choice agents against Trichomonas vaginalis. There are no other readily available medications to replace this class of drugs for the treatment of trichomonas infections. There are two research questions that need to be answered:
(1) Whether the treatment of pregnant women with symptoms (trichomonas vaginitis) is effective in reducing preterm birth.
(2) Whether the adverse effect of increased preterm birth in treated asymptomatic women with trichomonas observed in one, prematurely stopped trial is real.

POTENTIAL CONFLICT OF INTEREST

None known.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Klebanoff 2001
Methods	Double-blind randomized controlled trial using identical placebos. Randomization sequence was generated by computer. The method of allocation concealment and random allocation are not mentioned.
Participants	617 asymptomatic women in 15 centres in the USA. Women were screened from 8 weeks until 23 weeks and enrolled between 16 to 23 weeks. Exclusion criteria: increased vaginal discharge with symptoms, allergy to metronidazole, current ethanol abuse, antibiotic therapy within the previous 14 days, an intention to continue antenatal care or plan delivery outside catchment area, language barrier precluding informed consent, planned antibiotic therapy before delivery, current or planned cervical cerclage, preterm labor before screening, current or planned tocolytic therapy, fetal death, major congenital abnormality, multiple gestation, medical illness.
Interventions	Metronidazole 2g (250mg capsules x 8) on randomization + 2g after 48 hours repeated after 2 weeks versus placebo (lactose) capsules. The first treatment was before 23 weeks and the second between 24 to 29 weeks but at least 14 days after the initial treatment.
Outcomes	Preterm birth (<37 completed weeks) was the primary outcome.
Notes	- Two women were randomized without having trichomoniasis. - Compliance was around 80% in both groups.

	- 11.8% of all women were lost to follow-up. The authors report that the proportion of lost to follow-up was not significantly different between the two groups.
Allocation concealment	B – Unclear

Study	**Ross 1983**
Methods	Randomization was by alternate allocation. Placebos were not used. Technicians doing the parasitological assessments had no knowledge of the source of the specimens.
Participants	376 women attending a midwife operated antenatal clinic. Women were enrolled in two groups. The first group included those who booked before 34 weeks; the second group were initially uninfected but then found to be infected at 38 weeks. In each group women were randomly allocated to treatment (110 women) and no treatment (115 women) groups. 151 women were found not to be infected. This latter group was followed until delivery but not included in either group.
Interventions	Benzoylmetronidazole 50ml (2g metronidazole equivalent) oral, single dose vs no treatment. An extra dose of the medication was given to the women to take to their partners and they were asked to refrain from coitus until the follow-up visit. Untreated symptomatic patients received symptomatic relief but details of the agent used for symptomatic treatment are not given.
Outcomes	Perinatal outcome (mean birth weight, low birth weight). Gestational age at delivery Parasitological follow-up at one and four weeks.
Notes	Trichomoniasis was diagnosed by saline wetmount technique. - Loss to follow-up: 8/110 in metronidazole group lost at first control and a further 14 could not have outcome assessments because of delivery or loss to follow-up. In the no treatment group 5/115 were lost to follow-up and a further 19 attended too irregularly to assess parasitological diagnosis.
Allocation concealment	C – Inadequate

vs = versus

Characteristics of excluded studies

Study	**Reason for exclusion**
Robinson 1965	This trial was excluded because it was not clear whether the comparisons had been made between randomized groups. The authors extended a series of metronidazole treated pregnant and nonpregnant women to include a group of women randomly allocated to a treatment and placebo. Consequently, there is an imbalance in the sample sizes of two groups and it is not possible to identify randomised groups in the tables presented.
Roos 1978	There was no randomised comparison.

ANALYSES

Comparison 01. Metronidazole versus no treatment

Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Preterm birth (< 37 weeks)	1	604	Relative Risk (Fixed) 95% CI	1.78 [1.19, 2.66]
02 Low birth weight (< 2500 g)	1	604	Relative Risk (Fixed) 95% CI	1.38 [0.92, 2.06]
03 No parasitological cure	2	703	Relative Risk (Fixed) 95% CI	0.11 [0.08, 0.17]
05 Birth weight (kg)	1	208	Weighted Mean Difference (Fixed) 95% CI	-0.10 [-0.24, 0.04]
07 Gestational age (weeks)	1	200	Weighted Mean Difference (Fixed) 95% CI	-0.30 [-0.69, 0.09]

INDEX TERMS

Medical Subject Headings (MeSH)

Antiprotozoal Agents [*therapeutic use]; Metronidazole [therapeutic use]; Pregnancy Complications, Parasitic [*drug therapy]; Randomized Controlled Trials; Trichomonas Vaginitis [*drug therapy]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

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Authors	Gülmezoglu AM
Contribution of author(s)	Information not supplied by author
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Contact address	Dr A Metin Gülmezoglu Scientist UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) Department of Reproductive Health and Research World Health Organization Geneva 27 1211 SWITZERLAND E-mail: gulmezoglum@who.int Tel: +41 22 7913417 Fax: +41 22 7914171
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Analysis 01.01. Comparison 01 Metronidazole versus no treatment, Outcome 01 Preterm birth (< 37 weeks)

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Comparison: 01 Metronidazole versus no treatment

Outcome: 01 Preterm birth (< 37 weeks)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Klebanoff 2001	60/315	31/289		100.0	1.78 [1.19, 2.66]
Total (95% CI)	315	289		100.0	1.78 [1.19, 2.66]
Total events: 60 (Treatment), 31 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.79 p=0.005					

Analysis 01.02. Comparison 01 Metronidazole versus no treatment, Outcome 02 Low birth weight (< 2500 g)

Review: Interventions for trichomoniasis in pregnancy

Comparison: 01 Metronidazole versus no treatment

Outcome: 02 Low birth weight (< 2500 g)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Klebanoff 2001	51/315	34/289		100.0	1.38 [0.92, 2.06]
Total (95% CI)	315	289		100.0	1.38 [0.92, 2.06]
Total events: 51 (Treatment), 34 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.55 p=0.1					

Analysis 01.03. Comparison 01 Metronidazole versus no treatment, Outcome 03 No parasitological cure

Review: Interventions for trichomoniasis in pregnancy

Comparison: 01 Metronidazole versus no treatment

Outcome: 03 No parasitological cure

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Klebanoff 2001	20/269	168/260		74.6	0.12 [0.07, 0.18]
Ross 1983	6/83	61/91		25.4	0.11 [0.05, 0.24]
Total (95% CI)	352	351		100.0	0.11 [0.08, 0.17]

Total events: 26 (Treatment), 229 (Control)

Test for heterogeneity chi-square=0.02 df=1 p=0.89 I^2 =0.0%

Test for overall effect z=11.29 p<0.00001

Analysis 01.05. Comparison 01 Metronidazole versus no treatment, Outcome 05 Birth weight (kg)

Review: Interventions for trichomoniasis in pregnancy

Comparison: 01 Metronidazole versus no treatment

Outcome: 05 Birth weight (kg)

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Ross 1983	99	3.10 (0.49)	109	3.20 (0.54)		100.0	-0.10 [-0.24, 0.04]
Total (95% CI)	99		109			100.0	-0.10 [-0.24, 0.04]

Test for heterogeneity: not applicable

Test for overall effect z=1.40 p=0.2

Analysis 01.07. Comparison 01 Metronidazole versus no treatment, Outcome 07 Gestational age (weeks)

Review: Interventions for trichomoniasis in pregnancy

Comparison: 01 Metronidazole versus no treatment

Outcome: 07 Gestational age (weeks)

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Ross 1983	91	39.50 (1.50)	109	39.80 (1.30)		100.0	-0.30 [-0.69, 0.09]
Total (95% CI)	91		109			100.0	-0.30 [-0.69, 0.09]

Test for heterogeneity: not applicable

Test for overall effect z=1.50 p=0.1