Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery (Review)

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[Intervention review]

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

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ABSTRACT

Background

Preterm birth is birth before 37 weeks' gestation. Genital tract infection is one of the causes of preterm birth. Infection screening during pregnancy has been used to reduce preterm birth. However, infection screening may have some adverse effects, e.g. increased antibiotic drug resistance, increased costs of treatment.

Objectives

To assess the effectiveness and complications of antenatal lower genital tract infection screening and treatment programs in reducing preterm birth and subsequent morbidity.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2008) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 2).

Selection criteria

We included all published and unpublished randomised controlled trials in any language that evaluated any described methods of antenatal lower genital tract infection screening compared with no screening. Preterm births have been reported as an outcome.

Data collection and analysis

Two review authors independently assessed eligibility, trial quality and extracted data.

Main results

One study (4155 women) met the inclusion criteria. This trial is of high methodological quality. In the intervention group (2058 women), the results of infection screening and treatment for bacterial vaginosis, trichomonas vaginalis and candidiasis were reported; in the control group (2097 women), the results of the screening program for the women allocated to receive routine antenatal care were not reported. Preterm birth before 37 weeks was significantly lower in the intervention group (3% versus 5% in the control group)

with a relative risk (RR) of 0.55 (95% confidence interval (CI) 0.41 to 0.75). The incidence of preterm birth for low birthweight preterm infants with a weight equal to or below 2500 g and very low birthweight infants with a weight equal to or below 1500 g were significantly lower in the intervention group than in the control group (RR 0.48, 95% CI 0.34 to 0.66 and RR 0.34; 95% CI 0.15 to 0.75, respectively).

Authors' conclusions

There is evidence that infection screening and treatment programs in pregnant women may reduce preterm birth and preterm low birthweights. Future trials should evaluate the effects of types of infection screening program, gestational ages at screening test and the costs of introducing an infection screening program.

PLAIN LANGUAGE SUMMARY

Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

A genital tract infection during pregnancy can cross into the amniotic fluid and result in prelabour rupture of the membranes and preterm labour. Such infections include bacterial vaginosis; chlamydial, trichomonas and gonorrhoeal infections; syphilis and HIV, but not candida. Preterm birth (before 37 weeks of gestation) is associated with poor infant health and early deaths, admission of the newborn to neonatal intensive care in the first few weeks of life, prolonged hospital stay and long-term neurologic disability including cerebral palsy.

The present systematic review found that a simple infection screening and treatment program during routine antenatal care may reduce preterm births and preterm low (below 2500 g) and very low (below 1500 g) birthweights, from only one identified controlled study. The study was of high methodological quality and reported on 4155 women randomly assigned either to an intervention group where the results of infection screening were reported or a control group where the results of the vaginal smear test were not reported. The simple infection screening reduced preterm births from 5% of women in the control group to 3% in the intervention group. The number of low birthweight preterm infants and very low birthweight infants were significantly lower in the intervention group than in the control group. Neonatal morbidity or deaths in the hospitalisation period were not reported. No adverse effects were reported for the pregnant women during the treatment. Women in the intervention group who were found to have vaginal infection received standard treatment and blinding of the treatment was not possible. The obstetricians may, therefore, have provided a different level of care to women in whom an infection had been identified compared with the control group.

BACKGROUND

Preterm birth, defined as birth occurring prior to 37 weeks' gestation, occurs in 5% to 10% of all pregnancies and is the most common cause of perinatal morbidity and mortality in the world. Moreover, preterm birth is implicated in at least two-thirds of early infant deaths (Cunningham 1997) and causes 60% of perinatal mortality and nearly half of long-term neurologic disability, including cerebral palsy, and is associated with admission to neonatal intensive care, severe morbidity in the first weeks of life, prolonged hospital stay after birth, and readmission to hospital in the first year of life (Cunningham 2001; Goldenberg 1998; Roberts 2000; Wood 2000). Surviving infants, especially those born before 32 weeks, have a substantially increased risk of chronic lung disease, and major and minor impairments (Doyle 1996; Saigal 2000). Whatever the result, the emotional impact on the family can be enormous.

A wide spectrum of causes and demographic factors have been implicated in the birth of preterm infants. These can be categorized into four groups:

1. medical and obstetric complications: there are associations with placental hemorrhage and hypertensive disorders in about one-third of cases (Meis 1995);

2. lifestyle factors: there is an association with alcohol abuse, low maternal age, and occupational factors (Henriksen 1995; Holzman 1995; Satin 1994);

3. amniotic fluid infection caused by a variety of micro-organisms located in the genital tract: approximately one-third of preterm births are associated with chorioamniotic infection (Lettieri 1993); and

4. asymptomatic cervical dilatation (Papiernik 1986).

Many micro-organisms cause both symptomatic and asymptomatic infection and may result in preterm prelabour rupture of membranes, preterm labour, or both. For example, bacterial vaginosis (including *Gardnerella vaginalis*, *Bacteroides* species, *Mobiluncus* species, Ureaplasma urealyticum, and Mycoplasma hominis) (Hillier 1995; McDonald 1994; McGregor 1990; Meis 1995), Chlamydia trachomatis (Gravett 1986), Trichomonas vaginalis (Cotch 1997), Neisseria gonorrhoeae (Elliott 1990), Group B streptococci (Regan 1981), Staphylococcus aureus (McGregor 1990), syphilis (McFarlin 1995), HIV (Temmerman 1994), enteropharyngeal bacteria and Peptostreptococcus species (McDonald 1994) have been associated with an increased risk of preterm birth. Candida species, however, has not been associated with preterm birth (Cotch 1998).

A possible mechanism for the link between infection and preterm birth is the bacterial stimulation of the biosynthesis of prostaglandins, either directly via phospholipase $A_2$and C (Bejar 1981) or bacterial endotoxin introduced into the amniotic fluid stimulating decidual cells to produce cytokines and prostaglandins that initiate labour (Cox 1989). Indirect links via substances such as interleukin-1, tumour necrosis factor and platelet activating factor, all of which may be found in infected amniotic fluid, have also been identified (Romero 1992; Yoon 2000).

A program of screening for and treating asymptomatic vaginal infections has been associated with a reduction in preterm birth (Kiss 2006). There are differences in the screening methods of

different types of organisms. There is scant evidence that can be used to determine the optimal screening regimen appropriate for each organism in pregnancy. Therefore, it is unclear whether all women should be routinely screened, how often the screening should occur, and which tests should be used.

Chlamydia trachomatis has been identified by multiple tests from different specimen sources. The tests may be analysed by three types of DNA-based test: ligase chain reaction, polymerase chain reaction (PCR) and enzyme immuno-assay (Watson 2002). DNA amplification techniques are providing highly sensitive and specific tests (Black 1997). The screening test can detect Chlamydia on genital secretions, urine specimens, endocervical and vaginal or urethral samples (Domeika 1999; Shrier 2004). Nucleic acid amplification tests are more sensitive than cell culture (Jespersen 2005).

Trichomoniasis may be asymptomatic in up to 50% of infected women (Wolner-Hanssen 1989). The diagnosis is usually made on clinical findings and laboratory procedures (Petrin 1998) such as direct microscopy and culture. The gold standard for diagnosis of trichomoniasis is a culture (Borchardt 1991). Most frequently, the saline wet-mount preparation is used for observation of motile organisms under the light microscope. Wet-mount smear is a cheap and quick method but more sensitive techniques are culture, immunofluorescence and enzyme immunoassay (Lossick 1991). Different staining techniques include Gram stain, Giemsa stain, Papanicolaou smear, acridine orange (Borchardt 1991; Rein 1990), and diverse molecularly-based diagnostic methods (hybridization assay and PCR). These vary widely in sensitivities and specificities for screening Trichomoniasis (DeMeo 1996; Madico 1998; Mayta 2000; Muresu 1994).

Bacterial vaginosis is a clinical syndrome; the microbiology of bacterial vaginosis is complex and is composed of Gardnerella vaginalis, Mycoplasma hominis and anaerobic bacteria (Amsel 1983). The diagnosis is usually made on clinical Amsel criteria findings (Amsel 1983) and laboratory tests. Vaginal pH testing may be a valuable screening tool as it is a quick and inexpensive test (Gjerdingen 2000). Vaginal swab Gram stain with quantification of the microbial flora has high sensitivity and specificity and is accepted as an alternative method (Nugent 1991).

Screening tests for other organisms including syphilis have been identified by multiple tests. Screening tests such as Treponema pallidum hemagglutination assay, Treponema pallidum particle agglutination assay, and enzyme-linked immunosorbent assays (ELISAs) are more reliable than Venereal Disease Research Laboratory testing, the fluorescent treponemal antibody absorption test, and immunoblot assays (Muller 2006). The screening test for Neisseria gonorrhoeae, usually made from a culture, remains accurate when transport conditions are suitable. The tests could be used with cervical, urine and vaginal swabs. DNA amplification techniques provide highly sensitive and specific tests (Carroll 1998; Koumans 1998; Livengood 2001). Diagnosis of HIV infection can be obtained from enzyme-linked immunosorbent assay (ELISA), Western blot, and RNA PCR testing (Kleinman 1998). The HIV-p24 Ag was tested for early diagnosis of an acute HIV infection (Thies 1994). Strategies for the diagnosis of Group B streptococcus (GBS) include obtaining vaginal or both vaginal and anorectal GBS cultures (Quinlan 2000) and a rapid enrichment cum antigen detection test (Das 2003).

Other Cochrane protocols and reviews have addressed a number of issues regarding treatment of infection in pregnancy. Antibiotic treatment of chlamydial, trichomonas, bacterial vaginosis and gonorrhoeal infection in pregnancy appears to be effective to clear organisms (Brocklehurst 1998; Brocklehurst 2002; Gülmezoglu 2002; McDonald 2007) but it is not known whether treatment of trichomonas will have any effect on pregnancy outcomes (Gülmezoglu 2002). There is little evidence to show that screening and treatment in all asymptomatic pregnant women for bacterial vaginosis can prevent preterm birth (McDonald 2007). Antibiotic prophylaxis in pregnancies with a previous preterm birth associated with bacterial vaginosis can reduce preterm delivery (Thinkhamrop 2002). There is insufficient evidence to treat ureaplasmas to reduce preterm birth (Raynes-Greenow 2004). There is no evidence that antiretrovirals and the treatment of syphilis influence the incidence of premature delivery (Volmink 2007; Walker 2001). None of these reviews are concerned primarily with the screening program for antenatal lower genital tract infection. There is unclear evidence for the effectiveness of screening programs of lower genital tract infection to prevent preterm birth.

OBJECTIVES

To assess the effectiveness and complications of antenatal lower genital tract infection screening and treatment programs in reducing preterm birth and subsequent morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published and unpublished randomised controlled trials evaluating any described method of antenatal lower genital tract infection screening.

Types of participants

Pregnant women with a gestational age of less than 37 weeks, who are not in labour, have no vaginal bleeding and are without symptoms of lower genital tract infection.

Types of interventions

Any lower genital tract infection screening and treatment programs compared with no screening. The infection screening programs are defined as screening tests such as wet mount, Gram stain and culture of vaginal secretions and are followed by appropriate treatment after a positive screening test, or a screening test followed by no treatment after a negative screening test. No screening is defined as pregnant women receiving routine antenatal care but without being given a screening program.

Types of outcome measures

Primary outcomes

1. Preterm birth (less than 37 weeks)

Secondary outcomes

1. Low birthweight (LBW) less than 2500 g
2. Very LBW less than 1500 g (not prespecified)
3. Neonatal morbidity: sepsis, respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, seizures
4. Duration of admission to neonatal intensive care unit or hospital
5. Death: stillbirth, neonatal mortality, infant mortality
6. Side-effects of treatment including drug resistance
7. Persistent infection
8. Recurrent infection
9. Failure of treatment
10. Economic analysis (cost effectiveness, cost utility)
11. False positive/negative result of the screening program
12. Women's satisfaction

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Groups Trials Register by contacting the Trials Search Co-ordinator (January 2008).

The Cochrane Pregnancy and Childbirth Groups 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. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly 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 'Specialized Register section within the editorial information about the Cochrane Pregnancy and Childbirth Group. Trials identified through the searching activities described above are assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched the CENTRAL (*The Cochrane Library 2007,* Issue 2) using the search strategy detailed in Appendix 1

Searching other resources

We did not identify any additional or ongoing trials from personal communication. We searched the reference lists of trials and review articles identified.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Using the inclusion criteria, one review author, Ussanee Swadpanich (US),assessed all studies for inclusion in the review, and a second author, Witoon Prasertcharoensook (WP), independently duplicated the process. There were no disagreements.

Data extraction and management

We used the Cochrane Pregnancy and Childbirth Group's data extraction template to extract data. Both authors extracted the data using the agreed form. There were no discrepancies. We used the Review Manager software (RevMan 2003) to enter the data.

If any of the information regarding any of the above was inadequate, we attempted to contact authors of the original reports to provide further details.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We have described the methods used for generation of the randomisation sequence for the trial in the 'Characteristics of included studies' table.

(1) Selection bias (randomisation and allocation concealment)

We assigned a quality score for each trial, using the following criteria:

(A) adequate concealment of allocation: such as telephone randomisation, consecutively numbered, sealed opaque envelopes;

(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;

(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants - for example, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.
We will exclude the trials that have more than 20% loss of participants because of the risk of bias.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:
(1) blinding of participants (yes/no/unclear);
(2) blinding of caregiver (yes/no/unclear);
(3) blinding of outcome assessment (yes/no/unclear).
The one identified trial scored an A when rating selection bias and attrition bias.

Measures of treatment effect

We carried out statistical analysis using RevMan 2003. We presented dichotomous results as summary relative risks with 95% confidence intervals (CIs).
If we had identified more than one trial for continuous outcomes (such as duration of admission to neonatal intensive care unit or hospital), we would have presented weighted mean difference with 95% CIs if the outcomes were measured in the same way between trials. We would have used the standardised mean difference to combine trials that measured the same outcome, but used different methods. We would have conducted a fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If heterogeneity had been found, we would have explored this by a sensitivity analysis followed by random-effects if required.
If we find more trials in the future, we will use the methods we prespecified in the published protocol: *see* Table 1.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
The searches identified three potential publications. Two trials (Gjerdingen 2000; McGregor 1995) were excluded due to the participants not meeting the inclusion criteria and not being randomised controlled trials (*see* table of 'Characteristics of excluded studies').
One included article (Kiss 2004) reported a randomised controlled trial designed to evaluate a vaginal infection screening strategy for prevention of preterm delivery in a general population of pregnant women. A total of 4155 pregnant women presenting for their routine prenatal visit without subjective complaints were randomised to either the intervention (n = 2058) or the control group (n = 2097). All women were screened by Gram stain for asymptomatic vaginal infection. For the intervention group, women found to have vaginal infection received standard treatment. For the control group, vaginal smear test results were not revealed so the standard antenatal care program could not be influenced.

Risk of bias in included studies

Of the 4429 pregnant women who were randomised, 274 were excluded (140 lost to follow up; 68 did not fulfil all the inclusion criteria; 66 had multiple pregnancies).
Blinding of the treatment was not possible in the intervention group, but the vaginal smears were diagnosed in a central laboratory using the Nugent scoring system (Nugent 1991). This method of blinding permitted the risk of detection bias; the obstetricians may have provided a different level of care to women in the intervention group in whom an infection had been identified.

Effects of interventions

We identified a single randomised controlled trial comparing antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery with no screening program. A total of 4429 women were randomised with 274 women excluded from the analysis. In the intervention group (2058 women), the results of infection screening and treatment for bacterial vaginosis, trichomonas vaginalis and candidiasis were reported; in the control group (2097 women), the results of the screening program for the women allocated to receive routine antenatal care were not reported. There was a statistically significant difference for preterm birth before 37 weeks between the two groups (relative risk (RR) 0.55, 95% confidence interval (CI) 0.41 to 0.75).
For secondary outcomes, preterm low birthweight infants (weight equal to or below 2500 g) and preterm very low birthweight infants (weight equal to or below 1500 g) were significantly lower in the intervention group than in the control group (RR 0.48, 95% CI 0.34 to 0.66 and RR 0.34, 95% CI 0.15 to 0.75, respectively). None of the women reported adverse effects during the treatment period.

DISCUSSION

There is currently only one trial that meets our inclusion criteria (Kiss 2004) The results indicate statistically significant

lower preterm births in the intervention (screening and treatment) group. Low birthweight preterm births (below 2500 g) and very low birthweight (below 1500 g) were also significantly reduced in the intervention group. There was no information about adverse effects.

The results of this review are based on the evidence from one trial, assessed as being of high quality according to allocation concealment (see 'Methodological quality of included studies'). The strength of this review was that the included trial was a large multicentre prospective, randomized controlled trial. There was a clear sample-size calculation and an adequate number of participants were available for the analysis. However, around 3.2% of all randomized women (140/4429) were lost to follow up without the information of whether the loss to follow up rate was balance between the two groups. Not blinding participants and outcome assessors might create bias in providing different care between the two groups.

The included trial was conducted in a developed country (Austria) where characteristics of the population, e.g., incidences and pattern of lower genital tract infections and socioeconomic status, etc, might be different from other countries. Therefore, the results of this review might not be generalized to all pregnant women. Further trials in different population especially in developing countries are needed to confirm the results.

AUTHORS' CONCLUSIONS

Implications for practice

Integrating a simple infection screening and treatment program into routine antenatal care may reduce preterm births in a general population of pregnant women. However, based on the evidence reviewed, we are not able to determine the effects of recurrent or persistent infection on preterm birth. Healthcare providers should discuss the potential benefits and harms of infection screening and tailor them to meet the specific needs of each care setting and healthcare system, or both.

Implications for research

Further randomised controlled trials are needed to determine:

(1) the effects of infection screening programs (at different gestational ages, types of infection screening, number of screening test, in different population, e.g. developing countries);

(2) provide an economic analysis of infection screening programs.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Kiss 2004

Methods	Randomised trial with allocation concealed according to computer-generated randomisation list. Participant blinding: control group only blinded to test results. Description of withdrawals: yes. Intention-to-treat analysis: not used.
Participants	4429 pregnant women (mean age 28.9, SD 5.6) presenting for routine prenatal visits between 15 and 19 weeks' gestation (mean 17, SD 1.6). Intervention group: 2058 pregnant women; control group: 2097 pregnant women. Inclusion criteria: gestational age 15-19 weeks without subjective complaints (e.g., contractions and vaginal bleeding). Exclusion criteria: clinical symptoms of vaginal infection, multiple pregnancies. Location: Vienna, Austria.
Interventions	Intervention group: vaginal smears (Gram stain and evaluated by the scoring criteria proposed by Nugent 1991) screening for Bacterial vaginosis, Trichomonas vaginalis and Candida species and received standard antibiotic treatment if positive screening test, i.e., 2% for six days local clindamycin for bacterial vaginosis, 300 mg twice daily for seven days oral clindamycin for recurrent bacterial vaginosis, 0.1 g for six days local clotrimazole for candidiasis, and 500 mg for seven days local metronidazole for trichomoniasis and included treatment of the partner. Control group: were smeared, but the results of testing were not made available to the women's care providers and did not have any effect on the standard clinical antenatal care program routine antenatal examination.
Outcomes	Primary outcome: spontaneous preterm delivery GA less than 37 weeks. Secondary outcomes: 1. low birthweight: preterm birth with birthweights below 2500 g; 2. very low birthweight: preterm birth with birthweight below 1500 g; 3. rates of miscarriage between 16-22 and 20-24 weeks; 4. intrauterine death; 5. prevalence of various forms of vaginal infections; 6. duration of sick leave and hospitalisation.
Notes	4429 randomised, 274 excluded from analysis, 140 lost to follow up, 68 did not fulfil all inclusion criteria, 66 multiple pregnancies. We have contacted the author and are waiting for a reply for our request for additional data (secondary outcomes e.g. neonatal necrotizing enterocolitis, neonatal sepsis, neonatal death, duration of neonatal admission to NICU/hospital) from the authors. We will incorporate these additional data, along with the economic data from a secondary report of this trial (Kiss 2006), in an update to the review.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

[a] GA: gestational age
NICU: neonatal intensive care unit
SD: standard deviation

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

Study	Reason for exclusion
Gjerdingen 2000	Participants did not meet inclusion criteria. Study compared standard prenatal care including routine inquiry about vaginal symptoms versus standard care supplemented by vaginal pH testing. Both arms had pregnant women who were diagnosed with lower genital tract infection and all participants received vaginal pH screening. Participants: 121 pregnant women with or without vaginal infection symptoms. Intervention: vaginal pH testing. Outcomes: bacterial vaginosis detection rate, preterm deliveries.
McGregor 1995	Methods not clearly described, but seems likely that this was not a randomised controlled trial. Described as a prospective observational trial. Participants: 1260 women. Intervention: lower genital tract micro-organisms screening (vaginal fluid enzyme; nonspecific protease, sialidase, phospholipase C, phospholipase A2). Outcomes: preterm birth, early pregnancy loss.

DATA AND ANALYSES

Comparison 1. Lower genital tract infection screening versus no screening

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth less than 37 weeks	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.75]
2 Preterm low birthweight (below or equal 2500 g)	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.34, 0.66]
3 Preterm very low birthweight (below or equal 1500 g)	1	4155	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.75]
4 Neonatal morbidity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Duration of admission to neonatal intensive care unit/hospital	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Neonatal death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Side-effects of treatment (including drug resistance)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Persistent infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Recurrent infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Economic analysis	0		Economic analysis (Fixed, 95% CI)	Not estimable
11 Faise positive/negative of the screening program	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Women's satisfaction	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

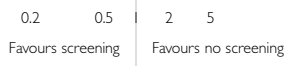
Analysis 1.1. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 1 Preterm birth less than 37 weeks.

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 1 Preterm birth less than 37 weeks

Study or subgroup	Infection screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kiss 2004	61/2058	112/2097		100.0 %	0.55 [0.41, 0.75]
Total (95% CI)	**2058**	**2097**		**100.0 %**	**0.55 [0.41, 0.75]**
Total events: 61 (Infection screening), 112 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.77 (P = 0.00016)					



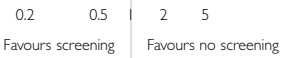
Analysis 1.2. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 2 Preterm low birthweight (below or equal 2500 g).

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 2 Preterm low birthweight (below or equal 2500 g)

Study or subgroup	infection screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kiss 2004	50/2058	107/2097		100.0 %	0.48 [0.34, 0.66]
Total (95% CI)	**2058**	**2097**		**100.0 %**	**0.48 [0.34, 0.66]**
Total events: 50 (infection screening), 107 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.40 (P = 0.000011)					



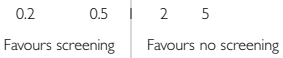
Analysis 1.3. Comparison 1 Lower genital tract infection screening versus no screening, Outcome 3 Preterm very low birthweight (below or equal 1500 g).

Review: Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery

Comparison: 1 Lower genital tract infection screening versus no screening

Outcome: 3 Preterm very low birthweight (below or equal 1500 g)

Study or subgroup	Infection screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kiss 2004	8/2058	24/2097		100.0 %	0.34 [0.15, 0.75]
Total (95% CI)	**2058**	**2097**		**100.0 %**	**0.34 [0.15, 0.75]**
Total events: 8 (Infection screening), 24 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.65 (P = 0.0080)					



APPENDICES

Appendix 1. CENTRAL search strategy

#1 Pregnancy (explode MeSH)
#2 Pregnancy Complications (explode MeSH)
#3 pregnan*
#4 (preterm or premature) near (labour or labor)
#5 Infection (explode MeSH)
#6 infect*
#7 Mass Screening (explode MeSH)
#8 screen*

#9 (#1 or #2 or #3 or #4)
#10 (#5 or #6)
#11 (7 or #8)
#12 (#9 and #10 and #11)

Appendix 2. Methods to be used

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials, in which the unit of randomisation was a group of participants rather than individual participants, in the analyses along with individually-randomised trials. Their sample sizes will be adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, this will be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis. Therefore, the meta-analysis will be performed in two parts as well.

Dealing with missing data

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Assessment of heterogeneity

We will apply tests of heterogeneity between trials, if appropriate, using the I-squared statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Subgroup analyses

If we have a large number of trials included, we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. We are aware of different screening methods and treatment practices for the same micro-organisms. If we have a large number of included trials, we will do subgroup analyses related to the same screening method following the same treatment practice for each type of organism. However, if we have a small number of trials, we will describe each trial with different screening and treatment practices separately.
We plan to carry out the following subgroup analyses:
(a) studies which screened and treated the same infection, e.g. bacterial vaginosis;
(b) types of abnormal vaginal flora compared with each other;
(c) recurrent infection versus persistent infection;
(d) singleton versus multiple pregnancy;
(e) gestational age at screening (less than 12, 13 to 27, 28 to 36 weeks);
(f) effect of treatment of various abnormal vaginal flora on preterm birth rate;
(g) low-income and high-income settings;
(h) screening following with treatment versus screening following without treatment.

Sensitivity analyses

We will carry out sensitivity analyses to explore the effect of trial quality. This will involve analyses based on an A, B, C, or D rating of selection bias and attrition bias. We will exclude studies of poor quality from the analyses (those rated B, C, or D) in order to assess any substantive difference to the overall result. We will then analyse the impact the inclusion of quasi-controlled trials has had on trial

quality. If cluster trials have been incorporated with an estimate of the ICC borrowed from a different trial, we will perform a sensitivity analysis to see what the effect of different values of the ICC on the results of the analysis would be.

WHAT'S NEW

Last assessed as up-to-date: 30 January 2008

Date	Event	Description
15 February 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

Ussanee Swadpanich (US) and Pisake Lumbiganon (PL): development of title and question.

US, PL and Witoon Prasertcharoensook (WP): developed the protocol.

Malinee Laopaiboon (ML): commented on drafts of the protocol.

PL: provided advice on the development of the protocol.

US: wrote the first draft of the review.

PL and ML: reviewed and gave comments on the drafts of the review.

Witoon Prasertcharoensook: commented on the drafts of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen Hospital, Khon Kaen, Ministry of Public Health, Thailand.
- Khon Kaen University, Faculty of Medicine, Khon Kaen, Thailand.
- Khon Kaen University, Faculty of Public Health, Thailand.

External sources

- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

INDEX TERMS

Medical Subject Headings (MeSH)

*Candidiasis, Vulvovaginal [diagnosis; therapy]; Premature Birth [etiology; *prevention & control]; *Trichomonas Vaginitis [diagnosis; therapy]; *Vaginosis, Bacterial [diagnosis; therapy]

MeSH check words

Female; Humans; Pregnancy