

Antenatal care

[T] Management of symptomatic vaginal discharge in pregnancy

NICE guideline <number>

Evidence reviews underpinning recommendations 1.4.7 to 1.4.11

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Draft for consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Management of symptomatic vaginal discharge in pregnancy

Review question

What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

Introduction

During normal pregnancy, most women will experience more vaginal discharge. If it is associated with symptoms such as itching, pain or an offensive smell it may be caused by an infection. Treating the infection may improve the woman's symptoms and her pregnancy outcomes. The aim of this review is to investigate what interventions are effective in the management of symptomatic vaginal discharge in pregnancy.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

| | |
|---------------------|---|
| Population | Pregnant woman with symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis |
| Intervention | <p>Group 1 Bacterial vaginosis</p> <ul style="list-style-type: none">• Vaginal antibiotics<ul style="list-style-type: none">○ Clindamycin cream○ Metronidazole cream• Oral antibiotics<ul style="list-style-type: none">○ Amoxicillin○ Clindamycin○ Metronidazole with or without erythromycin <p>Group 2 Vaginal trichomoniasis</p> <ul style="list-style-type: none">• Metronidazole <p>Group 3 Vaginal candidiasis</p> <ul style="list-style-type: none">• Antifungal treatment<ul style="list-style-type: none">○ Any imidazole antifungal vaginal cream (for example, miconazole, clotrimazole, terconazole, econazole)○ Oral fluconazole○ Vaginal antifungal pessary (for example, nystatin, imidazole)• Probiotics (various strains of lactobacillus only)<ul style="list-style-type: none">○ Oral<ul style="list-style-type: none">▪ Food/dietary supplement▪ 'Live' yoghurt○ Vaginal<ul style="list-style-type: none">▪ 'Live' yoghurt▪ Cream▪ Pessary▪ Suppository |

| | |
|-------------------|--|
| | <ul style="list-style-type: none"> ○ Combined oral + intravaginal |
| Comparison | <ul style="list-style-type: none"> ● Any other within-group listed intervention ● Placebo ● No treatment |
| Outcome | <p>Critical</p> <ul style="list-style-type: none"> ○ Preterm rupture of membrane (before 37⁺⁰ weeks of pregnancy) ○ Preterm birth (birth before 37⁺⁰ weeks) <p>Important</p> <ul style="list-style-type: none"> ○ Rate of cure/Symptomatic relief (during pregnancy/time of symptoms) ○ Women's experience and satisfaction of care (whilst symptomatic) ○ Fetal death from 16 weeks of gestational age (including termination of pregnancy) or infant death up to 1 year chronological age. ○ Infant death up to 1 year chronological age |

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual 2014](#). Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

Clinical evidence

Included studies

Bacterial vaginosis

Two randomised controlled trials (RCTs) were included for the treatment of symptomatic vaginal discharge due to bacterial vaginosis in pregnant women (Duff 1991, Moniri 2009).

The included studies are summarised in Table 2.

One RCT compared 14-day course of oral antibiotic (amoxicillin) to placebo in pregnant women with symptomatic vaginal discharge due to bacterial vaginosis (Duff 1991), whilst 1 RCT compared a 7-day course of oral antibiotic (metronidazole) to no treatment (Moniri 2009).

One RCT was conducted in the USA (Duff 1991) and 1 RCT was conducted in Iran (Moniri 2009).

Vaginal trichomoniasis

There was no evidence identified on interventions to treat symptomatic vaginal discharge due to vaginal trichomoniasis.

Vaginal candidiasis

Two RCTs and 1 non-randomised controlled trial were included for the treatment of symptomatic vaginal discharge due to vaginal candidiasis in pregnant women (Abdelmonem 2012, Rubin 1980, Ruiz-Velasco 1978).

The included studies are summarised in Table 3.

One RCT compared a 6-day course of antifungal treatment (clotrimazole vaginal tablets and cream) to placebo (Ruiz-Velasco 1978). One RCT compared a 7-day course of antifungal treatment (econazole vaginal cream) to a 14-day course of treatment in black women only (Rubin 1980). One non-RCT compared a probiotic mixture (bee-honey and yogurt mixture applied vaginally) to antifungal treatment (tioconazole vaginal tablet) (Abdelmonem 2012).

One RCT was conducted in Mexico (Ruiz-Velasco 1978), 1 RCT was conducted in South Africa (Rubin 1980), and the non-RCT was conducted in Egypt (Abdelmonem 2012).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review and reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review is presented in Table 2 and Table 3.

Table 2: Characteristics of included studies for treatment of symptomatic vaginal discharge due to bacterial vaginosis

| Study ID Study type Country | Population Number of participants | Intervention | Comparison | Outcomes |
|-----------------------------------|---|---|---|---|
| Duff 1991 RCT USA | N=108 Pregnant women at 15-25 weeks gestation with diagnostic Gram stain and positive clinical findings for bacterial vaginosis ¹ | Oral antibiotic (Amoxicillin 500 mg 3 times a day for 14 days) | Placebo | <ul style="list-style-type: none"> Rate of cure |
| Moniri 2009 RCT Iran | N=120 Pregnant women at 20-34 weeks gestation with diagnostic Gram stain and positive clinical findings for bacterial vaginosis ¹ | Oral antibiotic (Metronidazole 500 mg twice daily for 7 consecutive days) | No treatment and uninformed of their bacterial vaginosis status | <ul style="list-style-type: none"> Preterm birth |

Notes: ¹, Clinical findings indicative of bacterial vaginosis were: thin grey homogenous discharge, vaginal pH>4.5, amine odour of vaginal fluid after addition of 10% potassium hydroxide, presence of clue cells on microscopic examination of vaginal fluid at high power (400x). Abbreviations: N: total number of women included; RCT: randomised controlled trial.

Table 3: Characteristics of included studies for treatment of symptomatic vaginal discharge due to vaginal candidiasis

| Study ID Study type Country | Population Number of participants | Intervention | Comparison | Outcomes |
|-------------------------------------|--|--|--|----------------|
| Abdelmonem 2012 Non-RCT Egypt | N=156 Pregnant women who have diagnostic Gram stain/culture and positive clinical findings for vulvo-vaginal candidiasis ¹ | Antifungal treatment (Local tioconazole 100 mg vaginal tablet once daily for 7 days) | Probiotic (Bee-honey and yogurt mixture applied vaginally twice daily for 7 days) | • Rate of cure |
| Rubin 1980 RCT South Africa | N=67 Pregnant women at ≤36 weeks who have complaints of vaginal discharge and Gram stain/culture for vaginal candidiasis | Antifungal treatment (Econazole vaginal cream applied at night for 14 days) | Antifungal treatment (Discontinued treatment with econazole after 7 days then no treatment for 7 days) | • Rate of cure |
| Ruiz-Velasco 1978 RCT Mexico | N=100 Pregnant women at 32-36 weeks gestation who have positive clinical findings and cytology/culture for vaginal candidiasis | Antifungal treatment (Clotrimazole 100mg vaginal tablet and vulvar cream daily for 6 days) | Placebo tablets and inert cream for 6 days | • Rate of cure |

Notes: ¹, Positive clinical findings were itching, curd-like discharge and vulvo-vaginal redness on both gynaecological examination and self-reported history. Abbreviations: N: total number of women at randomisation; Non-RCT: non-randomised controlled trial; RCT(s): randomised controlled trial(s).

See the full evidence tables in appendix D and the forest plots in appendix E.

1 **Quality assessment of clinical outcomes included in the evidence review**

2 See the clinical evidence profiles in appendix F.

3 **Economic evidence**

4 **Included studies**

5 A systematic review of the economic literature was conducted but no economic studies were
6 identified which were applicable to this review question.

7 A single economic search was undertaken for all topics included in the scope of this
8 guideline. See supplementary material 2 for details.

9 **Excluded studies**

10 Economic studies not included in this review are listed, and reasons for their exclusion are
11 provided in appendix K.

12 **Summary of studies included in the economic evidence review**

13 No economic studies were identified which were applicable to this review question.

14 **Economic model**

15 No economic modelling was undertaken for this review because the committee agreed that
16 other topics were higher priorities for economic evaluation.

17 **Clinical evidence statements**

18 **Bacterial vaginosis**

19 ***Comparison 1. Oral antibiotic versus placebo***

20 **Critical outcomes**

21 **Preterm rupture of membrane**

22 No evidence was identified to inform this outcome.

23 **Preterm birth**

24 No evidence was identified to inform this outcome.

25 **Important outcomes**

26 **Rate of cure/Symptomatic relief**

- 27 • Moderate quality evidence from 1 RCT (N=81) showed that there is a clinically important
28 difference favouring oral antibiotic (amoxicillin) over placebo on rate of microbiologic cure
29 2 weeks after treatment in pregnant women with symptomatic vaginal discharge due to
30 bacterial vaginosis: RR 2.15 (95% CI 1.04 to 4.46).

31 **Women's experience and satisfaction of care**

32 No evidence was identified to inform this outcome.

1 **Fetal death from 16 weeks of gestational age**

2 No evidence was identified to inform this outcome.

3 **Infant death up to 1 year chronological age**

4 No evidence was identified to inform this outcome.

5 ***Comparison 2. Oral antibiotic versus no treatment***

6 **Critical outcomes**

7 **Preterm rupture of membrane**

8 No evidence was identified to inform this outcome.

9 **Preterm birth**

- 10 • Low quality evidence from 1 RCT (N=120) showed that there is no clinically important
11 difference between oral antibiotic (metronidazole) and no treatment on preterm birth in
12 pregnant women with symptomatic vaginal discharge due to bacterial vaginosis after 7
13 days treatment: RR 1.00 (95%CI 0.15 to 6.87).

14 **Important outcomes**

15 **Rate of cure/Symptomatic relief**

16 No evidence was identified to inform this outcome.

17 **Women's experience and satisfaction of care**

18 No evidence was identified to inform this outcome.

19 **Fetal death from 16 weeks of gestational age**

20 No evidence was identified to inform this outcome.

21 **Infant death up to 1 year chronological age**

22 No evidence was identified to inform this outcome.

23 **Vaginal candidiasis**

24 ***Comparison 3. Antifungal treatment versus placebo***

25 **Critical outcomes**

26 **Preterm rupture of membrane**

27 No evidence was identified to inform this outcome.

28 **Preterm birth**

29 No evidence was identified to inform this outcome.

30 **Important outcomes**

31 **Rate of cure/Symptomatic relief**

- 32 • Low quality evidence from 1 RCT (N=100) showed a clinically important difference
33 favouring antifungal treatment (clotrimazole vaginal tablet and cream) over placebo on
34 rate of mycological cure after 6 days treatment in pregnant women with symptomatic
35 vaginal discharge due to vaginal candidiasis: RR 1.52 (95% CI 1.17 to 1.96).

1 **Women's experience and satisfaction of care**

2 No evidence was identified to inform this outcome.

3 **Fetal death from 16 weeks of gestational age**

4 No evidence was identified to inform this outcome.

5 **Infant death up to 1 year chronological age**

6 No evidence was identified to inform this outcome.

7 ***Comparison 4. Antifungal treatment versus probiotic***

8 **Critical outcomes**

9 **Preterm rupture of membrane**

10 No evidence was identified to inform this outcome.

11 **Preterm birth**

12 No evidence was identified to inform this outcome.

13 **Important outcomes**

14 **Rate of cure/Symptomatic relief**

15 *Clinical cure rate*

- 16 • Very low quality evidence from 1 non-randomised controlled trial (N=129) showed no
17 clinically important difference between antifungal treatment (local tioconazole tablet) and
18 probiotics (bee-honey and yoghurt mixture) on the clinical cure rate after 7 days of
19 treatment in pregnant women with symptomatic vaginal candidiasis: RR 0.82 (95% CI
20 0.68 to 1.00).

21 *Mycological cure rate*

- 22 • Very low quality evidence from 1 non-randomised controlled trial (N=129) showed no
23 clinically important difference between antifungal treatment (local tioconazole tablet) and
24 probiotics (bee-honey and yoghurt mixture) on the mycological cure rate after 7 days of
25 treatment in pregnant women with symptomatic vaginal candidiasis: RR 1.19 (95% CI
26 1.03 to 1.38).

27 **Women's experience and satisfaction of care**

28 No evidence was identified to inform this outcome.

29 **Fetal death from 16 weeks of gestational age**

30 No evidence was identified to inform this outcome.

31 **Infant death up to 1 year chronological age**

32 No evidence was identified to inform this outcome.

33 ***Comparison 5. Antifungal treatment: 14 days versus 7 days***

34 **Critical outcomes**

35 **Preterm rupture of membrane**

36 No evidence was identified to inform this outcome.

1 **Preterm birth**

2 No evidence was identified to inform this outcome.

3 **Important outcomes**

4 **Rate of cure/Symptomatic relief**

- 5 • Very low quality evidence from 1 RCT (N=57) showed that there is a clinically important
6 difference favouring a 7-day course of antifungal treatment (econazole vaginal cream)
7 over a 14-day course of treatment on the rate of cure in pregnant women with
8 symptomatic vaginal candidiasis: RR 0.64 (95% CI 0.43 to 0.94).

9 **Women's experience and satisfaction of care**

10 No evidence was identified to inform this outcome.

11 **Fetal death from 16 weeks of gestational age**

12 No evidence was identified to inform this outcome.

13 **Infant death up to 1 year chronological age**

14 No evidence was identified to inform this outcome.

15 **Economic evidence statements**

16 No economic studies were identified which were applicable to this review question.

17 **The committee's discussion of the evidence**

18 **Interpreting the evidence**

19 ***The outcomes that matter most***

20 Preterm rupture of membrane and preterm birth were considered to be critical outcomes
21 because vaginal infection during pregnancy may be associated with preterm birth. The
22 outcomes of rate of cure and symptomatic relief were considered as important outcomes
23 because they indicate whether a treatment is effective. Women's experience and satisfaction
24 of care was also an important outcome because women's views and experience are central
25 to how they are cared for. Perinatal and infant mortality were considered as important rather
26 than critical outcomes because the committee considered it to be indirect consequence of
27 vaginal infection rather than of the interventions themselves.

28 ***The quality of the evidence***

29 The quality of the evidence on the use of oral antibiotics to treat symptomatic vaginal
30 discharge due to bacterial vaginosis ranged from moderate to low quality. For the
31 comparison of oral antibiotics versus placebo, the outcome of rate of mycological cure at 2
32 weeks follow up was of moderate quality due to imprecision of the effect estimate. No
33 evidence was identified for preterm rupture of membrane, preterm birth, women's experience
34 and satisfaction of care, fetal death or infant death. For the comparison of oral antibiotics
35 versus no treatment, the quality of evidence on the outcome of preterm birth was low due to
36 imprecision of the effect estimate. No evidence was identified for preterm rupture of
37 membrane, rate of cure/symptom relief, women's experience and satisfaction of care, fetal
38 death or infant death. No evidence was identified for the use of vaginal antibiotics nor on the
39 use of oral clindamycin in pregnant women with symptomatic vaginal discharge due to
40 bacterial vaginosis.

1 The quality of the evidence on the use of antifungal treatment (clotrimazole tablet/cream) to
2 treat symptomatic vaginal discharge due to vaginal candidiasis ranged from low to very low.
3 For the comparison of antifungal treatment versus placebo, the quality of evidence for the
4 outcome of mycological cure after 6 days of treatment was moderate quality due to serious
5 overall risk of bias and imprecision in the effect estimate. No evidence was identified for
6 preterm rupture of membrane, preterm birth, women's experience and satisfaction of care,
7 fetal death or infant death. For the comparison of antifungal treatment (tioconazole tablet)
8 versus probiotics, the outcome of clinical and mycological cure were both of very low quality
9 due to serious risk of bias, indirectness (it was unclear whether the probiotic mixture used
10 'live' lactobacillus) and imprecision of the effect estimate. No evidence was identified for
11 preterm rupture of membrane, preterm birth, women's experience and satisfaction of care,
12 fetal death or infant death. For the comparison of a 14-day course versus a 7-day course of
13 antifungal treatment (econozale cream), the outcome of mycological cure rate was of very
14 low quality due to serious overall risk of bias, indirectness (the trial was conducted in 1990, in
15 a sample of Black African women only) and imprecision in the effect estimate. No evidence
16 was identified for preterm rupture of membrane, preterm birth, women's experience and
17 satisfaction of care, fetal death or infant death.

18 No relevant evidence was identified on treatment of symptomatic vaginal discharge due to
19 vaginal trichomoniasis.

20 ***Benefits and harms***

21 The committee agreed that there is a need to balance the potential benefit of treating
22 infections causing symptomatic vaginal discharge to the potential harm the treatment could
23 cause. The committee also agreed that it is important to consider the harm of overusing
24 antimicrobial therapies which may lead to antimicrobial resistance. Overall, the committee
25 agreed that the evidence for the treatment of symptomatic vaginal discharge due to bacterial
26 vaginosis, vaginal trichomoniasis, or vaginal candidiasis is very limited. The limited evidence
27 suggested that antibiotics and antifungal treatment are likely effective in treating the
28 symptoms/infection, however, it is not known whether the use of antibiotics, antifungals, or
29 probiotics to treat symptomatic vaginal discharge caused by an infection pose a risk to the
30 pregnant women or the baby.

31 **Information about vaginal discharge**

32 Some pregnant women who have vaginal discharge may find it distressing or uncomfortable.
33 The committee therefore agreed, using their knowledge and experience, to recommend that
34 pregnant women be reassured that vaginal discharge is a normal physiological change
35 during pregnancy, however, they should also be made aware that when there are other
36 symptoms associated with the vaginal discharge, this may indicate an infection. Depending
37 on the situation, this may warrant investigations and treatment.

38 **Appropriate investigations**

39 Symptomatic vaginal discharge can be caused by a variety of infections, including bacterial
40 vaginosis, trichomoniasis, candidiasis or sexually transmitted infections such as chlamydia.
41 The committee agreed that sometimes the clinical picture is clear and there is no need to
42 conduct investigations to confirm the cause of the symptoms. However, the committee
43 agreed, using their knowledge and experience, that it was important that a recommendation
44 is made that when the cause of symptomatic discharge is not clinically obvious, appropriate
45 investigations should be considered. In many cases this means a vaginal swab test. When
46 there is a concern that the symptomatic vaginal discharge could be due to sexually
47 transmitted infection, appropriate investigations should be considered so that it can be
48 appropriately managed and the risk to the woman and the baby posed by untreated
49 infections be mitigated.

1 **Antibiotic treatment for bacterial vaginosis**

2 Overall, the committee recognised that the evidence on the benefits and harms of antibiotics
3 for treatment of symptomatic vaginal discharge due to bacterial vaginosis was very limited,
4 with only two RCTs identified and limited outcomes reported. The committee noted that it is
5 common practice to prescribe vaginal or oral antibiotics – in particular, vaginal clindamycin or
6 oral metronidazole - and therefore agreed, using their knowledge and experience, that a
7 general recommendation for the use of antibiotics should be made. The committee also
8 recognised that there is a substantial body of evidence that antibiotics are effective in the
9 asymptomatic population – that is, women who are known to have bacterial vaginosis but
10 who do not have any symptoms – but that they could not assume that they were clinically
11 effective in the symptomatic population.

12 For the comparison of oral antibiotic versus placebo, one RCT conducted in pregnant women
13 showed that the probability of mycological cure in participants who received oral amoxicillin
14 for 14 days was 2.15 times as high as the probability of cure in those who received placebo
15 (41% vs 19% cured, respectively) at two-weeks follow up. However, this study did not report
16 any other outcomes of interest to provide a more comprehensive view of the benefits and
17 harms. However, the committee noted that the study was small, conducted over 30 years
18 ago, and that the use of oral amoxicillin to treat vaginal discharge due to bacterial vaginosis
19 is not common in current practice in the UK. The committee were also aware that there is
20 some suggestion that amoxicillin use in the first trimester may be associated with an
21 increased risk of oral clefts in babies.

22 For the comparison of oral antibiotic versus no treatment, one RCT found that there was no
23 difference in preterm birth between pregnant women who received a 7-day course of oral
24 metronidazole and those who received no treatment, with less than 4% of the sample (2% in
25 each arm) giving birth before 37+0 weeks. No other outcomes were reported by the study so
26 the overall picture of benefits and harms is uncertain.

27 **Antifungal treatment for vaginal candidiasis**

28 The evidence on the use of antifungal and probiotics to treat symptomatic vaginal discharge
29 due to vaginal candidiasis was limited, with all 3 studies only reporting the outcome of rate of
30 cure. The committee noted that all the included studies used vaginal imidazole-based
31 antifungal treatments and that they were effective on the outcome of mycological cure with
32 over 80% of women in the antifungal groups having a negative culture after treatment.

33 One RCT found that pregnant women who received vaginal clotrimazole tablets and cream
34 were more likely to be cured after 6 days treatment, as assessed by mycological tests,
35 compared to placebo tablet and cream. This study did not report any other benefits and
36 harms of interest.

37 One non-RCT found no important difference in clinical or mycological cure rate between
38 women who received vaginal tioconazole tablets and those who applied a bee honey and
39 yoghurt mixture vaginally. This study did not report any other benefits and harms of interest.
40 The committee noted some women may prefer treatment with probiotics rather than
41 antifungals. However, the non-randomised controlled study was at serious overall risk of bias
42 and did not specify the strain of lactobacillus used in the study. Given this, and since there
43 are over 180 species of lactobacillus, the committee agreed that no recommendation about
44 the use of probiotics could be made.

45 Finally, one RCT compared a 14-day course of antifungal treatment (vaginal econazole
46 cream) to a 7-day course followed by no treatment for 7 days and found that women in the
47 14-day group were less likely to be mycologically cured than those in the 7-day group at the
48 end of treatment. No other benefits and harms of interest were reported in this study. The
49 committee noted that it is common practice to prescribe a 7-day course of vaginal antifungal

- 1 treatment and that there was not sufficient evidence to further specify duration of antifungal
2 treatment.
- 3 Based on the evidence that antifungal treatments were effective, the committee agreed to
4 recommend offering imidazole to women with symptomatic vaginal discharge due to vaginal
5 candidiasis. Since the various vaginal imidazoles examined by the studies can be assumed
6 to have a similar mechanism of action, the committee agreed to recommend a vaginal
7 imidazole and not a specific type of imidazole, although they recognised that not all types of
8 imidazole are used for treating vaginal candidiasis.
- 9 **Cost effectiveness and resource use**
- 10 No economic studies were identified which were applicable to this review question.
- 11 These recommendations reinforce current practice and there is unlikely to be any impact on
12 resource use or costs.

1 **References**

2 **Abdelmonem 2012**

3 Abdelmonem, A. M., Rasheed, S. M., Mohamed, A. S., Bee-honey and yogurt: A novel
4 mixture for treating patients with vulvovaginal candidiasis during pregnancy, Archives of
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14 other vaginal discharges, S Afr Med JSouth African medical journal = Suid-Afrikaanse
15 tydskrif vir geneeskunde, 57, 407-8, 1980.

16 **Ruiz-Velasco 1978**

17 Ruiz-Velasco V, Rosas-Arceo J. Prophylactic clotrimazole treatment to prevent mycoses
18 contamination of the newborn. International Journal of Gynaecology and Obstetrics;16:70–1,
19 1978.

1 Appendices

2 Appendix A – Review protocols

3 **Table 4: Review protocol for review question: What interventions are effective in treating symptomatic vaginal discharge**
 4 **due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy?**

| Field (based on PRISMA-P) | Content |
|--|--|
| Review question | What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy? |
| Type of review question | Intervention |
| Objective of the review | The aim of this review is to evaluate outcomes in women who have symptomatic vaginal discharge due to bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy, and to establish whether there are any harms for the mother or baby associated with them. |
| Eligibility criteria – population | Pregnant woman with symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis. |
| Eligibility criteria – intervention(s) | <p>Only the following listed interventions for each cause of vaginal discharge will be considered.</p> <p>Group 1 Bacterial vaginosis</p> <ul style="list-style-type: none"> • Vaginal antibiotics <ul style="list-style-type: none"> ○ Clindamycin cream ○ Metronidazole cream • Oral antibiotics <ul style="list-style-type: none"> ○ Amoxicillin ○ Clindamycin ○ Metronidazole with or without erythromycin <p>Group 2 Vaginal trichomoniasis</p> <ul style="list-style-type: none"> • Metronidazole <p>Group 3 Vaginal candidiasis</p> <ul style="list-style-type: none"> • Antifungal treatment <ul style="list-style-type: none"> ○ Any imidazole antifungal vaginal cream (for example, miconazole, clotrimazole, terconazole, econazole) ○ Oral fluconazole ○ Vaginal antifungal pessary (for example, nystatin, imidazole) • Probiotics (various strains of lactobacillus only) <ul style="list-style-type: none"> ○ Oral <ul style="list-style-type: none"> ▪ Food/dietary supplement ▪ 'Live' yoghurt |

| Field (based on PRISMA-P) | Content |
|--------------------------------------|---|
| | <ul style="list-style-type: none"> ○ Vaginal <ul style="list-style-type: none"> ▪ 'Live' yoghurt ▪ Cream ▪ Pessary ▪ Suppository ○ Combined oral + intravaginal |
| Eligibility criteria – comparator(s) | <ul style="list-style-type: none"> • Any other intra-class intervention (such as, within-group comparison) • Placebo • No treatment <p>Note: for the subgroup of vaginal candidiasis, the comparison of antifungal treatment combined with probiotics vs. only one of these treatments will be considered.</p> |
| Outcomes and prioritisation | <p>Critical</p> <ul style="list-style-type: none"> ○ Preterm rupture of membrane (before 37⁺⁰ weeks of pregnancy) ○ Preterm birth (birth before 37⁺⁰ weeks) <p>Important</p> <ul style="list-style-type: none"> ○ Rate of cure/Symptomatic relief (during pregnancy / time of symptoms) ○ Women's experience and satisfaction of care (whilst symptomatic) ○ Fetal death from 16 weeks of gestational age (including termination of pregnancy, and so on) ○ Infant death up to 1 year chronological age |
| Eligibility criteria – study design | <p>INCLUDE:</p> <ul style="list-style-type: none"> ○ Systematic reviews ○ Randomised or quasi-randomised controlled trials (individual or cluster) <p>If no evidence of these types is found for a listed intervention, the following types of studies in order of priority will be considered:</p> <ul style="list-style-type: none"> • Non-randomised (clinical) controlled trials (individual or cluster) • Prospective comparative observational cohort studies • Retrospective comparative observational cohort studies |
| Other inclusion exclusion criteria | <p>Exclusion</p> <p>POPULATION:</p> <ul style="list-style-type: none"> • Multiple pregnancy • Pregnancy with known or pre-existing congenital anomalies <p>STUDY DESIGN:</p> <ul style="list-style-type: none"> • Before-and-after studies • Case-control studies • Cross-over studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Interrupted time series studies • Non-comparative studies |

| Field (based on PRISMA-P) | Content |
|---|--|
| | <p>LANGUAGE:</p> <ul style="list-style-type: none"> Non-English <p>PUBLICATION STATUS:</p> <ul style="list-style-type: none"> Conference abstract <p>Inclusion</p> <p>COUNTRY:</p> <ul style="list-style-type: none"> No restriction |
| Proposed sensitivity/sub-group analysis, or meta-regression | <p>Subgroup analysis according to World Bank status (High-income countries; Low and middle-income countries) will be conducted (see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups for classification of countries). In the presence of heterogeneity, the following subgroup analyses will be conducted:</p> <ul style="list-style-type: none"> Gestational age by trimester at presentation of diagnosis Route of administration Duration of treatment (Single dose: ≤3 days, between 4 and 5 days, and >5 days) <p>Statistical heterogeneity will be assessed by visually examining the forest plots and by calculating the I² inconsistency statistic (with an I² value ≥50% indicating serious heterogeneity, and ≥80% indicating very serious heterogeneity).</p> |
| Selection process – duplicate screening/selection /analysis | <p>Studies included in the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) that satisfy the review protocol will be included in this review. Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.</p> |
| Data management (software) | <p>NGA STAR software will be used to generate bibliographies/citations, and conduct study sifting and data extraction. Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). For details please see supplement 1: methofs. 'GRADEpro' will be used to assess the quality of evidence for each outcome.</p> |
| Information sources – databases and dates | <p>Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase.</p> <p>Limits (for example, date, study design):</p> <ul style="list-style-type: none"> Date limit: 2006 (date of last search for CG62) Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results. |
| Identify if an update | <p>This antenatal care update will replace the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62), which will be taken down in due course. The following relevant recommendations in CG62 on treatment of vaginal discharge were made:</p> <p>1.4.6.1 Women should be informed that an increase in vaginal discharge is a common physiological change that occurs during pregnancy. If it is associated with itch, soreness, offensive smell or pain on passing urine there may be an infective cause and investigation should be considered.</p> <p>1.4.6.2 A 1-week course of a topical imidazole is an effective treatment and should be considered for vaginal candidiasis infections in pregnant women. 1.4.6.3 The effectiveness and safety of oral treatments for vaginal candidiasis in pregnancy are uncertain and these treatments should not be offered</p> |
| Author contacts | <p>Developer: National Guideline Alliance.</p> |
| Highlight if amendment to previous protocol | <p>For details please see section 4.5 of Developing NICE guidelines: the manual.</p> |

| Field (based on PRISMA-P) | Content |
|--|--|
| Search strategy – for one database | For details please see appendix B. |
| Data collection process – forms/duplicate | A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or G (economic evidence tables). |
| Data items – define all variables to be collected | For details please see evidence tables in appendix D (clinical evidence tables) or G (economic evidence tables). |
| Methods for assessing bias at outcome/study level | <p>Quality assessment of individual studies will be performed using the following checklists:</p> <ul style="list-style-type: none"> • ROBIS for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies <p>For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/.</p> |
| Criteria for quantitative synthesis (where suitable) | For details please see section 6.4 of Developing NICE guidelines: the manual. |
| Methods for analysis – combining studies and exploring (in)consistency | For details please see supplement 1: methods. |
| Meta-bias assessment – publication bias, selective reporting bias | For details please see supplement 1: methods and section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway. |
| Assessment of confidence in cumulative evidence | For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual. |
| Rationale/context – Current management | For details please see the introduction to the evidence review. |
| Describe contributions of authors and guarantor | A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Kate Harding in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see supplement 1: methods |

| Field (based on PRISMA-P) | Content |
|------------------------------|---|
| Sources of funding/support | The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. |
| Name of sponsor | The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. |
| Roles of sponsor | NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England. |
| PROSPERO registration number | This protocol is not registered with PROSPERO. |

1 CCTR: *Cochrane Controlled Trials Register*; CDSR: *Cochrane Database of Systematic Reviews*; CENTRAL: *Cochrane Central Register of Controlled Trials*; DARE: *Database*
 2 *of Abstracts of Reviews of Effects*; GRADE: *Grading of Recommendations Assessment, Development and Evaluation*; HTA: *Health Technology Assessment*; NGA: *National*
 3 *Guideline Alliance*; NICE: *National Institute for Health and Care Excellence*; NIHR: *National Institute for Health Research*; RCT(s): *randomised controlled trial(s)*; RoB: *risk of*
 4 *bias ROBIS: Risk Of Bias In Systematic reviews tool*; ROBINS-I: *Risk Of Bias In Non-randomized studies – of Interventions tool*.

5

Appendix B – Literature search strategies

Literature search strategies for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy?

Database(s): Medline & Embase (Multifile)

Last searched on **Embase Classic+Embase** 1947 to 2020 September 02, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to September 02, 2020

Date of last search: 3rd September 2020

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

| # | Searches |
|----|---|
| 1 | Pregnancy/ use ppez |
| 2 | Pregnant Women/ use ppez |
| 3 | pregnancy/ use emczd |
| 4 | pregnant woman/ use emczd |
| 5 | pregnan\$.tw. |
| 6 | 1 or 2 or 3 or 4 or 5 |
| 7 | *Obstetric Labor, Premature/ use ppez |
| 8 | *Pregnancy Complications, Infectious/ use ppez |
| 9 | *premature labor/ use emczd |
| 10 | *pregnancy complication/ use emczd |
| 11 | *prematurity/ use emczd |
| 12 | preterm.tw. |
| 13 | 7 or 8 or 9 or 10 or 11 or 12 |
| 14 | *Metronidazole/ or *Clindamycin/ or *Amoxicillin/ or *Miconazole/ or *Clotrimazole/ or *Econazole/ or *Imidazoles/ or *Nystatin/ or *Pessaries/ or *Fluconazole/ or Probiotics/ or exp Lactobacillus/ |
| 15 | 14 use ppez |
| 16 | *metronidazole/ or *clindamycin/ or *amoxicillin/ or *miconazole/ or *clotrimazole/ or *econazole/ or *imidazole/ or *terconazole/ or *nystatin/ or *vagina pessary/ or *fluconazole/ or probiotic agent/ or exp Lactobacillus/ |
| 17 | 16 use emczd |
| 18 | (metronidazole\$ or clindamycin\$ or amoxicillin\$ or miconazole\$ or clotrimazol\$ or econazol\$ or imidazole\$ or terconazol\$ or nystatin\$ or pessar\$ or fluconazole\$ or terconazol\$ or yoghurt\$ or probiotic\$ or lactobacillus\$.tw. |
| 19 | 15 or 17 or 18 |
| 20 | 13 and 19 |
| 21 | Vaginosis, Bacterial/ or *Vaginitis/ or Trichomonas Vaginitis/ or Candidiasis, Vulvovaginal/ or Candida/ or Candida albicans/ or Candidiasis/ or Candidiasis, Vulvovaginal/ |
| 22 | 21 use ppez |
| 23 | vaginitis/ or vaginal trichomoniasis/ or trichomonas vaginalis/ or *vulvovaginitis/ or candida/ or Candida albicans/ or candidiasis/ or vagina candidiasis/ |
| 24 | 23 use emczd |
| 25 | ((vagin\$ or vulvovagin\$) adj (trichomon\$ or candid\$)).tw. |
| 26 | (bacteria\$ adj vagin\$).tw. |
| 27 | (vagin\$ adj8 BV).tw. |
| 28 | candid\$.kw. |
| 29 | (abnormal\$ adj (vagin\$ or cervi\$) adj discharge\$).tw. |
| 30 | 22 or 24 or 25 or 26 or 27 or 28 or 29 |
| 31 | 6 and 30 |
| 32 | 20 or 31 |
| 33 | limit 32 to english language |
| 34 | limit 33 to yr="2006 -Current" |
| 35 | (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab. |
| 36 | crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti.ab. |
| 37 | meta-analysis/ |
| 38 | meta-analysis as topic/ |
| 39 | systematic review/ |

| # | Searches |
|----|--|
| 40 | meta-analysis/ |
| 41 | (meta analy* or metanaly* or metaanaly*).ti,ab. |
| 42 | ((systematic or evidence) adj2 (review* or overview*)).ti,ab. |
| 43 | ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. |
| 44 | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 45 | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 46 | (search* adj4 literature).ab. |
| 47 | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 48 | cochrane.jw. |
| 49 | ((pool* or combined) adj2 (data or trials or studies or results)).ab. |
| 50 | letter/ |
| 51 | editorial/ |
| 52 | news/ |
| 53 | exp historical article/ |
| 54 | Anecdotes as Topic/ |
| 55 | comment/ |
| 56 | case report/ |
| 57 | (letter or comment*).ti. |
| 58 | 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 |
| 59 | randomized controlled trial/ or random*.ti,ab. |
| 60 | 58 not 59 |
| 61 | animals/ not humans/ |
| 62 | exp Animals, Laboratory/ |
| 63 | exp Animal Experimentation/ |
| 64 | exp Models, Animal/ |
| 65 | exp Rodentia/ |
| 66 | (rat or rats or mouse or mice).ti. |
| 67 | 60 or 61 or 62 or 63 or 64 or 65 or 66 |
| 68 | letter.pt. or letter/ |
| 69 | note.pt. |
| 70 | editorial.pt. |
| 71 | case report/ or case study/ |
| 72 | (letter or comment*).ti. |
| 73 | 68 or 69 or 70 or 71 or 72 |
| 74 | randomized controlled trial/ or random*.ti,ab. |
| 75 | 73 not 74 |
| 76 | animal/ not human/ |
| 77 | nonhuman/ |
| 78 | exp Animal Experiment/ |
| 79 | exp Experimental Animal/ |
| 80 | animal model/ |
| 81 | exp Rodent/ |
| 82 | (rat or rats or mouse or mice).ti. |
| 83 | 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 |
| 84 | 67 use ppez |
| 85 | 83 use emczd |
| 86 | 84 or 85 |
| 87 | 35 use ppez |
| 88 | 36 use emczd |
| 89 | 87 or 88 |
| 90 | (or/37-38,41,43-48) use ppez |
| 91 | (or/39-42,44-49) use emczd |
| 92 | 90 or 91 |
| 93 | 34 and 86 |
| 94 | 34 not 93 |
| 95 | 89 or 92 |
| 96 | 94 and 95 [RCT/SR data] |
| 97 | 94 not 96 [Non-RCT/SR data] |

Database(s): Cochrane Library

Last searched on **Cochrane Database of Systematic Reviews**, Issue 9 of 12, September 2020, **Cochrane Central Register of Controlled Trials**, Issue 9 of 12, September 2020
Date of last search: 3rd September 2020

| # | Searches |
|-----|---|
| #1 | MeSH descriptor: [Pregnancy] this term only |
| #2 | MeSH descriptor: [Pregnant Women] this term only |
| #3 | (pregnan*):ti,ab,kw |
| #4 | #1 OR #2 OR #3 |
| #5 | MeSH descriptor: [Obstetric Labor, Premature] this term only |
| #6 | MeSH descriptor: [Pregnancy Complications, Infectious] this term only |
| #7 | (preterm):ti,ab,kw |
| #8 | #5 or #6 or #7 |
| #9 | MeSH descriptor: [Metronidazole] this term only |
| #10 | MeSH descriptor: [Clindamycin] this term only |
| #11 | MeSH descriptor: [Amoxicillin] this term only |
| #12 | MeSH descriptor: [Miconazole] this term only |
| #13 | MeSH descriptor: [Clotrimazole] this term only |
| #14 | MeSH descriptor: [Econazole] this term only |
| #15 | MeSH descriptor: [Imidazoles] this term only |
| #16 | MeSH descriptor: [Nystatin] this term only |
| #17 | MeSH descriptor: [Pessaries] this term only |
| #18 | MeSH descriptor: [Fluconazole] this term only |
| #19 | MeSH descriptor: [Probiotics] this term only |
| #20 | MeSH descriptor: [Lactobacillus] explode all trees |
| #21 | ((metronidazole* or clindamycin* or amoxicillin* or miconazole* or clotrimazole* or econazole* or imidazole* or terconazole* or nystatin* or pessar* or fluconazole* or terconazole* or yoghurt* or probiotic* or lactobacillus*)):ti,ab,kw |
| #22 | #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 |
| #23 | MeSH descriptor: [Vaginosis, Bacterial] this term only |
| #24 | MeSH descriptor: [Vaginitis] this term only |
| #25 | MeSH descriptor: [Trichomonas Vaginitis] this term only |
| #26 | MeSH descriptor: [Candidiasis, Vulvovaginal] this term only |
| #27 | MeSH descriptor: [Candida] this term only |
| #28 | MeSH descriptor: [Candida albicans] this term only |
| #29 | MeSH descriptor: [Candidiasis] this term only |
| #30 | ((vagin* or vulvovagin*) NEXT (trichomon* or candid*)):ti,ab,kw |
| #31 | ((bacter* NEXT vagin*)):ti,ab,kw |
| #32 | ((vagin* NEAR/8 BV)):ti,ab,kw |
| #33 | (candid*):kw |
| #34 | ((abnormal* NEXT (vagin* or cervi*) NEXT discharge*)):ti,ab,kw |
| #35 | #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 |
| #36 | #8 AND #22 |
| #37 | #4 AND #35 |
| #38 | #36 OR #37 Publication Year from 2006 to current |

Database(s): CRD: Database of Abstracts of Reviews of Effects (DARE), HTA Database

Date of last search: 3rd September 2020

| # | Searches |
|----|---|
| 1 | MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES IN DARE,HTA |
| 2 | MeSH DESCRIPTOR Pregnant Women EXPLODE ALL TREES IN DARE,HTA |
| 3 | (pregnan*) IN DARE, HTA |
| 4 | #1 OR #2 OR #3 |
| 5 | MeSH DESCRIPTOR Vaginosis, Bacterial EXPLODE ALL TREES IN DARE,HTA |
| 6 | MeSH DESCRIPTOR Vaginitis EXPLODE ALL TREES IN DARE,HTA |
| 7 | MeSH DESCRIPTOR Trichomonas Vaginitis EXPLODE ALL TREES IN DARE,HTA |
| 8 | MeSH DESCRIPTOR Candidiasis, Vulvovaginal EXPLODE ALL TREES IN DARE,HTA |
| 9 | ((vagin* or vulvovagin*) NEAR (trichomon* or candid*)) IN DARE, HTA |
| 10 | ((bacter* vagin*)) IN DARE, HTA |
| 11 | ((vagin* NEAR BV)) IN DARE, HTA |
| 12 | ((abnormal* vagin* discharge*)) IN DARE, HTA |
| 13 | ((abnormal* cervi* discharge*)) IN DARE, HTA |
| 14 | #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 |
| 15 | #4 AND #14 |
| 16 | MeSH DESCRIPTOR Obstetric Labor, Premature EXPLODE ALL TREES IN DARE,HTA |
| 17 | MeSH DESCRIPTOR Pregnancy Complications, Infectious EXPLODE ALL TREES IN DARE,HTA |
| 18 | (preterm) IN DARE, HTA |
| 19 | #16 OR #17 OR #18 |
| 20 | MeSH DESCRIPTOR Metronidazole EXPLODE ALL TREES IN DARE,HTA |
| 21 | MeSH DESCRIPTOR Clindamycin EXPLODE ALL TREES IN DARE,HTA |
| 22 | MeSH DESCRIPTOR Amoxicillin EXPLODE ALL TREES IN DARE,HTA |
| 23 | MeSH DESCRIPTOR Miconazole EXPLODE ALL TREES IN DARE,HTA |

| # | Searches |
|----|---|
| 24 | MeSH DESCRIPTOR Clotrimazole EXPLODE ALL TREES IN DARE,HTA |
| 25 | MeSH DESCRIPTOR Econazole EXPLODE ALL TREES IN DARE,HTA |
| 26 | MeSH DESCRIPTOR Imidazoles EXPLODE ALL TREES IN DARE,HTA |
| 27 | MeSH DESCRIPTOR Nystatin EXPLODE ALL TREES IN DARE,HTA |
| 28 | MeSH DESCRIPTOR Pessaries EXPLODE ALL TREES IN DARE,HTA |
| 29 | MeSH DESCRIPTOR Fluconazole EXPLODE ALL TREES IN DARE,HTA |
| 30 | ((metronidazole* or clindamycin* or amoxicillin* or miconazole* or clotrimazol* or econazol* or imidazole* or terconazol* or nystatin* or pessar* or fluconazole* or terconazol* or yoghurt*)) IN DARE, HTA |
| 31 | #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 |
| 32 | #19 AND #31 |
| 33 | MeSH DESCRIPTOR Probiotics EXPLODE ALL TREES IN DARE,HTA |
| 34 | MeSH DESCRIPTOR Lactobacillus EXPLODE ALL TREES IN DARE,HTA |
| 35 | ((probiotic* or lactobacillus*)) IN DARE, HTA |
| 36 | #33 OR #34 OR #35 |
| 37 | #19 AND #36 |
| 38 | #15 OR #32 OR #37 Publication Year from 2006 to current |

Database(s): Cinahl Plus

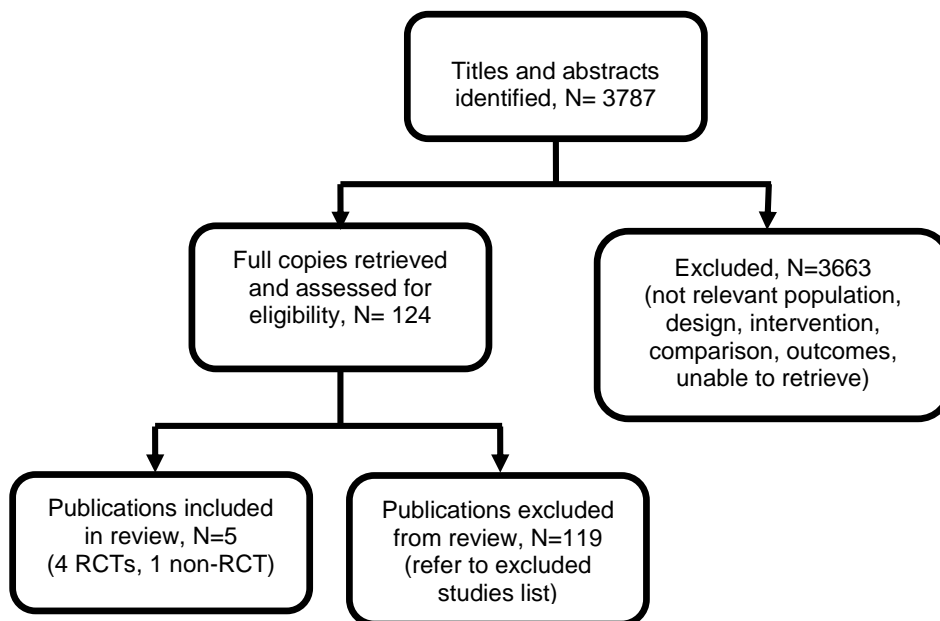
Date of last search: 3rd September 2020

| # | Searches |
|-----|--|
| S36 | S34 NOT S35 Limiters - Publication Year: 2006-2020; English Language; |
| S35 | PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website |
| S34 | S22 OR S33 |
| S33 | S4 AND S32 |
| S32 | S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 |
| S31 | TI (abnormal* N1 (vagin* or cervi*) N1 discharge*) OR AB (abnormal* N1 (vagin* or cervi*) N1 discharge*) |
| S30 | TI (vagin* N8 BV) OR AB (vagin* N8 BV) |
| S29 | TI (bacteria* N1 vagin*) OR AB (bacteria* N1 vagin*) |
| S28 | TI ((vagin* or vulvovagin*) N1 (trichomon* or candid*)) OR AB ((vagin* or vulvovagin*) N1 (trichomon* or candid*)) |
| S27 | (MH "Candida") OR (MH "Candida Albicans") OR (MH "Candidiasis") |
| S26 | (MM "Vaginitis") |
| S25 | (MH "Candidiasis, Vulvovaginal") |
| S24 | (MH "Trichomonas Vaginitis") |
| S23 | (MH "Vaginosis, Bacterial") |
| S22 | S8 AND S21 |
| S21 | S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 |
| S20 | TI (metronidazole* or clindamycin* or amoxicillin* or miconazole* or clotrimazol* or econazol* or imidazole* or terconazol* or nystatin* or pessar* or fluconazole* or terconazol* or yoghurt* or probiotic* or lactobacillus*) OR AB (metronidazole* or clindamycin* or amoxicillin* or miconazole* or clotrimazol* or econazol* or imidazole* or terconazol* or nystatin* or pessar* or fluconazole* or terconazol* or yoghurt* or probiotic* or lactobacillus*) |
| S19 | (MH "Lactobacillus+") |
| S18 | (MH "Probiotics") |
| S17 | (MM "Fluconazole") |
| S16 | (MM "Pessaries") |
| S15 | (MM "Nystatin") |
| S14 | (MM "Imidazoles") |
| S13 | (MM "Clotrimazole") |
| S12 | (MM "Miconazole") |
| S11 | (MM "Amoxicillin") |
| S10 | (MM "Clindamycin") |
| S9 | (MM "Metronidazole") |
| S8 | S5 OR S6 OR S7 |
| S7 | TI preterm or AB preterm |
| S6 | (MM "Pregnancy Complications, Infectious") |
| S5 | (MM "Labor, Premature") |
| S4 | S1 OR S2 OR S3 |
| S3 | TI pregnan* OR AB pregnan* |
| S2 | (MH "Expectant Mothers") |
| S1 | (MH "Pregnancy") |

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy?

Figure 1: PRISMA flow chart for review question:



Appendix D – Clinical evidence tables

Table 5: Clinical evidence tables for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy?

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|--|---|--|---|---|---|
| <p>Full citation</p> <p>Abdelmonem, A. M., Rasheed, S. M., Mohamed, A. S., Bee-honey and yogurt: A novel mixture for treating patients with vulvovaginal candidiasis during pregnancy, Archives of gynecology and obstetrics, 286, 109-114, 2012</p> <p>Ref Id</p> <p>903908</p> <p>Country/ies where the study was carried out</p> <p>Egypt</p> <p>Study type</p> <p>Non-randomised controlled trial</p> <p>Aim of the study</p> | <p>Sample size</p> <p>Intervention: N=94 (N=82 in final study group) Control: N=62 (N=47 in final study group)</p> <p>Characteristics</p> <p><u>Maternal age</u> Intervention: 35.0, SD 3.1 Control: 34.0, SD 2.8</p> <p><u>Parity</u> Intervention: 3.0, SD 1.7 Control: 3.0, SD 1.3</p> <p><u>BMI</u> Intervention: 25.4, SD 2.1 Control: 26.2, SD 3.2</p> <p><u>Itching before treatment - number (%)</u> Intervention: 39 (83.0) Control: 66 (80.5)</p> <p><u>Discharge before treatment - number (%)</u> Intervention: 35 (74.5) Control: 61 (74.4)</p> <p><u>Vulvo-vaginal redness - number (%)</u></p> | <p>Interventions</p> <p>Intervention: Antifungal treatment (local tioconazole 100 mg vaginal tablet once daily for 7 days). Control: Bee-honey and yogurt mixture applied vaginally twice daily for 7 days.</p> | <p>Details</p> <p>VVC diagnosed clinically (itching, curd-like discharge, and vulvo-vaginal redness) and laboratory (Gram staining and culture of the vaginal discharge). Follow-up visits were scheduled 1 week after treatment.</p> <p>Power analysis To achieve 80% power, 122 participants were required.</p> <p>Statistical analyses Clinical cure rates were compared between treatment groups using the Chi-square test. Continuous outcome data were compared using the Student <i>t</i>-test.</p> | <p>Results</p> <p>Important outcomes</p> <p>Rate of cure/Symptomatic relief (during pregnancy/time of symptoms)</p> <p><u>Clinical cure rate at 1 week FU - number (%)</u> Intervention: 34/47 (72.3) Control: 72/82 (87.8) p=0.02</p> <p><u>Mycological cure rate at 1 week FU - number (%)</u> Intervention: 43/47 (91.5) Control: 63/82 (76.9) p=0.01</p> | <p>Limitations</p> <p>Risk of Bias in Non-randomised studies-of Interventions: Bias due to confounding: Critical. (Study not randomised, participants allocated according to clinical diagnosis and result of Gram stain only. No information about allocation concealment). Bias in selection of participants into the study: Moderate. (Insufficient information regarding whether personnel were blinded). Bias in classification of interventions: Moderate. (Interventions groups clearly defined. Insufficient information regarding outcome assessors). Bias due to deviations from intended interventions: Low. (No deviations from intended interventions). Bias due to missing data: Critical. (17.3% dropouts). Bias in measurement of outcomes:</p> |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|--|---|---|---|
| <p>To assess compare the effects of bee-honey and yogurt versus local antifungal agents in the treatment of vulvo-vaginal candidiasis during pregnancy.</p> <p>Study dates July 2009 to July 2011.</p> <p>Source of funding Not stated.</p> | <p>Intervention: 32 (68.1) Control: 53 (64.6)</p> <p>No statistically significant difference between maternal age (34.0, SD 2.8 vs 35.0, SD 3.1), parity (3.0, SD 1.3 vs 3.0, SD 1.7) or body mass index (26.2, SD 3.2 vs 25.4, SD 2.1) between treatment groups.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> Pregnant women with vulvo-vaginal candidiasis (VVC). <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients with diabetes. Immuno-compromised patients. Patients who refused to share or dropped out during the follow-up period. | | | | <p>Moderate. (Insufficient information regarding whether personnel were blinded). Bias in selection of the reported result: Moderate. (Insufficient information, no protocol available). Other sources of bias: Low. (No baseline differences reported) Overall: Serious</p> <p>Other information Unclear whether yogurt was 'live' nor what stain of lactobacillus.</p> |
| Full citation | Sample size | Interventions | Details | Results | Limitations |
| Duff,P., Lee,M.L., Hillier,S.L., Herd,L.M., Krohn,M.A., Eschenbach,D.A., Amoxicillin treatment of bacterial | N=108 Intervention: N=54 (bacterial vaginosis present n=45; 9 women experienced | Intervention: Oral antibiotic (Amoxicillin 500 | After completion of treatment, between 34-36 weeks' gestation and at time of labour, a Gram-stained | Important outcomes Rate of cure/Symptomatic relief (during | Cochrane risk of bias tool V2: |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|--|--|--|--|--|---|
| <p>vaginosis during pregnancy, Obstetrics and Gynecology, 77, 431-435, 1991</p> <p>Ref Id</p> <p>128187</p> <p>Country/ies where the study was carried out</p> <p>USA</p> <p>Study type</p> <p>Randomised controlled trial (RCT)</p> <p>Aim of the study</p> <p>To examine the effectiveness of amoxicillin for bacterial vaginosis during pregnancy.</p> <p>Study dates</p> <p>May 1987 to September 1988.</p> <p>Source of funding</p> <p>Supported by the March of Dimes grant.</p> | <p>spontaneous resolution of infection prior to treatment) Control: N=54 (bacterial vaginosis present n=48; 6 women experienced spontaneous resolution of infection prior to treatment)</p> <p>Characteristics</p> <p>There was no significant difference between treatment groups in terms of maternal age, alcohol or tobacco use, history of vaginal infections and sexually transmitted diseases (no further data presented).</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Pregnant women (between 15 to 25 weeks of gestation); • Diagnostic Gram stain plus positive clinical findings*. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Women with penicillin allergy; | <p>mg three times daily for 14 days) Control: Placebo (three times daily for 14 days (containing lactose))</p> | <p>smear of vaginal fluid and specimen was evaluated for presence of infection.</p> <p>Power analysis Not stated.</p> <p>Statistical analyses Subgroup analysis was performed in women who complied with the study intervention. Compliance and side effects were compared between treatment groups and statistical significance was tested using the Yates-corrected X² test or Fisher exact test.</p> <p>Intention-to-treat (ITT) analysis Outcome analysis was performed on an ITT basis.</p> | <p>pregnancy/time of symptoms) <u>Gram stain - bacterial vaginosis absent at 2 weeks after treatment - number (%)</u> Intervention (n=39): 16 (41) Control (n=42): 8 (20)</p> | <p>Randomisation process: Low risk. (Adaptive randomisation plan using a biased-coin technique. Allocation concealed by each patient receiving an identification number and medication bottle).</p> <p>Deviations from intended interventions (assignment): Low risk. (Physician, study nurse, and participant blinded to medication).</p> <p>Missing outcome data: Some concerns. (Loss of follow-up was <20% in each group and the reasons were similar).</p> <p>Measurement of the outcome: Low risk. (Physician and study nurse blinded to medication).</p> <p>Selection of the reported result: Some concerns. (All outcomes reported, insufficient information). Other sources of bias: Low risk. (No other obvious sources of bias).</p> <p>Overall: Some concerns</p> <p>Other information</p> <p>*The diagnosis of bacterial vaginosis was assessed by Nugent criteria (7-</p> |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|--|--|--|---|--|--|
| | <ul style="list-style-type: none"> • Antimicrobial use within 2 weeks of enrolment; • Previous antimicrobial associated colitis; • Insulin-dependent diabetes mellitus; • Cervical cerclage; • Multiple gestation; • Hypertension requiring treatment; • Pregnancy-induced hypertension; • Fetal anomalies diagnosed before enrolment; • Gestational age greater than 25 weeks; • Anticipated movement away from the treatment area; • Inability to speak and read English. | | | | 10) and positive clinical signs (thin gray homogeneous discharge, pH greater than 4.5, amine odour of the vaginal fluid after addition of 10% potassium hydroxide and presence of clue cells on microscope examination of the vaginal fluid at high power. **Successful treatment was defined as the absence of bacterial vaginosis by Gram stain, microscopy and clinical examination. |
| Full citation Moniri, R., Behrashi, M., Effects of metronidazole therapy on preterm labor in women with bacterial vaginosis, Acta Medica Iranica, 47, 181-184, 2009 Ref Id | Sample size N=120 Intervention: N=60 Control: N=60 Characteristics <u>Maternal age (years) - mean ±SD</u> | Interventions Intervention: Oral antibiotic (Metronidazole 500 mg twice daily for 7 consecutive days) Control: No treatment | Details All women had similar healthcare management throughout pregnancy (public healthcare system). Women in control group were not informed of their bacterial vaginosis test results during trial period. Power analysis | Results Critical outcomes Pre-term birth (birth before 37⁺⁰ weeks) - number (%) Intervention: 2/60 (3.3) Control: 2/60 (3.3) | Limitations Cochrane risk of bias tool V2: Randomisation process: Some concerns. (No details provided, insufficient information on randomisation process and allocation concealment). Deviations from intended interventions (assignment): |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|-----------------------------|--|----------------------------------|---|
| <p>411196</p> <p>Country/ies where the study was carried out</p> <p>Iran</p> <p>Study type</p> <p>Randomised controlled trial.</p> <p>Aim of the study</p> <p>To assess the effects of metronidazole on preterm labour in the treatment of pregnant women with symptomatic bacterial vaginosis.</p> <p>Study dates</p> <p>March 2002 to October 2002.</p> <p>Source of funding</p> <p>Supported by a research grant from Deputy for Researches, Kashan University of Medical Sciences and Health Services, Iran.</p> | <p>Intervention: 25.7 (6.4) Control: 27.6 (5.6)</p> <p><u>Maternal weight (kg) - mean ±SD</u></p> <p>Intervention: 73 (0.1) Control: 72 (0.4)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> Pregnant women between 20 and 34 weeks of gestational age. Bacterial vaginosis confirmed with homogeneous, greyish-white discharge, gram staining of vaginal secretions, vaginal pH >4.5, clue cells on saline wet mount, positive whiff-amine test. <p>Exclusion criteria</p> <p>Not stated.</p> | | <p>Not stated.</p> <p>Statistical analyses</p> <p>Survival analysis conducted using chi-square test and Fisher's exact tests.</p> <p>Intention-to-treat (ITT) analysis</p> | | <p>High risk. (Clinicians and participants in the control group were not told of their diagnosis, but women with bacterial vaginosis and their clinicians were aware of their diagnosis).</p> <p>Missing outcome data: Low risk. (No reported loss to follow up in either arm).</p> <p>Measurement of the outcome: Some concerns. (No details provided on outcome assessors, insufficient information).</p> <p>Selection of the reported result: Some concerns. (Protocol not available, insufficient information). Other sources of bias: Low risk. (No other obvious sources of bias)</p> <p>Overall: Some concerns</p> |
| Full citation | Sample size | Interventions | Details | Results | Limitations |
| Rubin, A., Russell, J. M., Mauff, A., Efficacy of | N=67 Intervention: N=35 | Intervention: Antifungal | Participants applied econazole for 7 days, after | <u>Important outcomes</u> | |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|--|--|---|--|--|
| <p>econazole in the treatment of candidiasis and other vaginal discharges, S Afr Med J South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 57, 407-8, 1980</p> <p>Ref Id</p> <p>913684</p> <p>Country/ies where the study was carried out</p> <p>South Africa</p> <p>Study type</p> <p>Randomised trial.</p> <p>Aim of the study</p> <p>To assess the efficacy of econazole in the treatment of pregnant women with candidiasis and other vaginal discharges.</p> <p>Study dates</p> <p>February to October 1978.</p> <p>Source of funding</p> <p>Unclear (potential funding from Squibb Laboratories).</p> | <p>Control: N=32</p> <p>Characteristics</p> <p>All participants were black pregnant women.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> Pregnant women with complaints of vaginal discharge and positive culture. <p>Exclusion criteria</p> <ul style="list-style-type: none"> Pregnant women who had recently been treated with antibiotics. Women >36 weeks' pregnancy. | <p>treatment for 14 days (Econazole vaginal cream applied at night)</p> <p>Control: Antifungal treatment for 7 days (Econazole vaginal cream applied for 7 days at night, then no treatment for 7 days).</p> | <p>which one group (chosen at random) discontinued treatment while a second group continued treatment for a further 7 days.</p> <p>Statistical analyses</p> <p>Not stated.</p> | <p>Rate of cure/Symptomatic relief (during pregnancy/time of symptoms)</p> <p><u>Negative culture - number (%)</u></p> <p>Intervention: 16/31 (45.7)</p> <p>Control: 21/26 (65.6)</p> | <p>Cochrane risk of bias tool V2:</p> <p>Randomisation process: Some concerns. (No details provided, insufficient information).</p> <p>Deviations from intended interventions (assignment): Some concerns. (No details provided, insufficient information).</p> <p>Missing outcome data: Some concerns. (Loss of follow-up was <20%).</p> <p>Measurement of the outcome: Some concerns. (No details provided, insufficient information).</p> <p>Selection of the reported result: Some concerns. (No protocol available, insufficient information).</p> <p>Other sources of bias: Some concerns. (During the 7 days of no treatment, participants in control group may have had continued effects from treatment period)</p> <p>Overall: High risk</p> |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|--|--|---|---|---|---|
| <p>Full citation</p> <p>Ruiz-Velasco, V., Rosas-Arceo, J., Prophylactic clotrimazole treatment to prevent mycoses contamination of the newborn, Int J Gynaecol Obstet International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 16, 70-1, 1978</p> <p>Ref Id</p> <p>913685</p> <p>Country/ies where the study was carried out</p> <p>Mexico</p> <p>Study type</p> <p>Randomised trial.</p> <p>Aim of the study</p> <p>To assess the effectiveness of clotrimazole treatment in pregnant women to prevent morbidity in the newborn.</p> | <p>Sample size</p> <p>Intervention: N=50 Control: N=50</p> <p>Characteristics</p> <p>Authors stated that both treatment groups were similar for age, weight, number of previous pregnancies and percentage of primiparae.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Women between 32 and 36 weeks pregnancy. • Vaginal moniliasis, confirmed by means of clinical data, fresh examinations, cytology and culture of the genital exudate. <p>Exclusion criteria</p> <p>Not stated.</p> | <p>Interventions</p> <p>Intervention: Antifungal treatment (Clotrimazole 0.1 g vaginal tablets and vulvar cream for 6 days). Control: Placebo tablets and inert cream (for 6 days)</p> | <p>Details</p> <p>Power analysis Not stated. Statistical analyses Not stated. Intention-to-treat (ITT) analysis Not stated.</p> | <p>Results</p> <p>Important outcomes Rate of cure/Symptomatic relief (during pregnancy/time of symptoms) Negative culture of vaginal exudate Intervention: 44/50 (88%) Control: 29/50 (58%)</p> | <p>Limitations</p> <p>Cochrane risk of bias tool V2: Randomisation process: Some concerns. (No details provided, insufficient information). Deviations from intended interventions (assignment): Some concerns. (No details provided, insufficient information). Missing outcome data: Some concerns. (No details provided, insufficient information). Measurement of the outcome: Some concerns. (No details provided, insufficient information). Selection of the reported result: Some concerns. (No protocol available, insufficient information). Other sources of bias: Low risk. (No other obvious sources of bias) Overall: High risk</p> |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|--------------|---------------|---------|----------------------|----------|
| <p>Study dates Not stated.</p> <p>Source of funding Not stated.</p> | | | | | |

BMI: body mass index; FU: follow-up; SD: standard deviation

Appendix E – Forest plots

Forest plots for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy?

There are no forest plots for this review as no meta-analysis was conducted.

Appendix F – GRADE tables

Full GRADE tables for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy?

Table 6: Clinical evidence profile for oral antibiotic versus placebo for symptomatic vaginal discharge due to bacterial vaginosis

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|-------------------|-------------------------|--------------------------|-------------------------|----------------------|----------------------|-----------------|------------|------------------------|---|---------------|------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Oral antibiotic | Placebo | Relative (95% CI) | Absolute | | |
| Rate of mycological cure - At 2 weeks FU - Oral amoxicillin in pregnant women (follow-up 2 weeks; assessed with: Gram stain) | | | | | | | | | | | | |
| 1 (Duff 1991) | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious ¹ | none | 16/39 (41%) | 8/42 (19%) | RR 2.15 (1.04 to 4.46) | 219 more per 1000 (from 8 more to 659 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |

CI: confidence interval; FU: follow-up; RR: risk ratio

¹ Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

Table 7: Clinical evidence profile for oral antibiotic versus no treatment for symptomatic vaginal discharge due to bacterial vaginosis

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|--|-------------------|-------------------------|--------------------------|-------------------------|---------------------------|----------------------|-----------------|--------------|---------------------|--|----------|------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Oral antibiotic | No treatment | Relative (95% CI) | Absolute | | |
| Preterm birth – Oral metronidazole (assessed with: Birth before 37+0 weeks) | | | | | | | | | | | | |
| 1 (Moniri 2009) | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious ¹ | none | 2/60 (3.3%) | 2/60 (3.3%) | RR 1 (0.15 to 6.87) | 0 fewer per 1000 (from 28 fewer to 196 more) | ⊕⊕○○ LOW | IMPORTANT |

CI: confidence interval; RR: risk ratio

¹ Evidence downgraded by 2 levels because 95% CI crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

Table 8: Clinical evidence profile for antifungal treatment versus placebo for symptomatic vaginal discharge due to vaginal candidiasis

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|-------------------|----------------------|--------------------------|-------------------------|----------------------|----------------------|----------------------|-------------|------------------------|--|----------|------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Antifungal treatment | Placebo | Relative (95% CI) | Absolute | | |
| Rate of mycological cure - Clotrimazole vaginal tablet and cream versus placebo vaginal tablet and cream (assessed with: Negative culture of vaginal exudate after 6 days) | | | | | | | | | | | | |
| 1 (Ruiz-Velasco 1978) | randomised trials | serious ¹ | no serious inconsistency | no serious indirectness | serious ² | none | 44/50 (88%) | 29/50 (58%) | RR 1.52 (1.17 to 1.96) | 302 more per 1000 (from 99 more to 557 more) | ⊕⊕○○ LOW | IMPORTANT |

CI: confidence interval; RR: risk ratio

1 Evidence downgraded by 1 level due to serious overall risk of bias: Unclear risk of bias for selection bias, performance bias, attrition bias, and other bias.

2 Evidence downgraded by 1 level because 95% CI crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

Table 9: Clinical evidence profile for antifungal treatment versus probiotics for symptomatic vaginal discharge due to vaginal candidiasis

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|--|----------------------------------|----------------------|--------------------------|----------------------|----------------------|----------------------|----------------------|---------------|------------------------|---|---------------|------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Antifungal treatment | Probiotics | Relative (95% CI) | Absolute | | |
| Rate of cure - Clinical cure (follow-up 1 weeks; assessed with: Absence of itching and discharge) | | | | | | | | | | | | |
| 1 (Abdelmonem 2012) | non-randomised controlled trials | serious ¹ | no serious inconsistency | serious ² | serious ³ | none | 34/47 (72.3%) | 72/82 (87.8%) | RR 0.82 (0.68 to 1.0) | 158 fewer per 1000 (from 281 fewer to 0 more) | ⊕○○○ VERY LOW | |
| Rate of cure - Mycological cure (follow-up 1 weeks; assessed with: Negative culture for candida albicans) | | | | | | | | | | | | |
| 1 (Abdelmonem 2012) | non-randomised controlled trials | serious ¹ | no serious inconsistency | serious ² | serious ³ | none | 43/47 (91.5%) | 63/82 (76.8%) | RR 1.19 (1.03 to 1.38) | 146 more per 1000 (from 23 more to 292 more) | ⊕○○○ VERY LOW | |

CI: confidence interval; RR: risk ratio

1 Evidence downgraded by 1 level due to serious overall risk of bias: critical level of bias due to confounding; moderate level of bias in selection of participants into the study; moderate level of bias in classification of interventions; low level of bias due to deviations from intended interventions; critical level of bias due to missing data; moderate level of bias in measurement of outcomes; moderate risk of bias in selection of the reported result; and low risk of other sources of bias.
 2 Evidence downgraded by 1 level because it is unclear whether the probiotic mixture contained live lactobacillus and no details provided about strain used.
 3 Evidence downgraded by 1 level because 95% CI crosses 1 default MID (0.8 or 1.25).

Table 10: Clinical evidence profile for antifungal treatment for 14 days versus antifungal treatment for 7 days for symptomatic vaginal discharge due to vaginal candidiasis

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|--|-------------------|----------------------|--------------------------|----------------------|----------------------|----------------------|----------------------------------|---------------------------------|------------------------|---|------------------|------------|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Antifungal treatment for 14 days | Antifungal treatment for 7 days | Relative (95% CI) | Absolute | | |
| Rate of mycological cure (assessed with: Negative culture 14 days after start of trial) | | | | | | | | | | | | |
| 1 (Rubin 1980) | randomised trials | serious ¹ | no serious inconsistency | serious ² | serious ³ | none | 16/31 (51.6%) | 21/26 (80.8%) | RR 0.64 (0.43 to 0.94) | 291 fewer per 1000 (from 48 fewer to 460 fewer) | ⊕○○○ VERY LOW | CRITICAL |

CI: confidence interval; RR: risk ratio

1 Evidence downgraded by 1 level due to serious overall risk of bias: Unclear risk of bias for selection bias, performance bias, other sources of bias). Participants in control group may have had continued effects from treatment period during the 7 days in which they did not receive any treatment.
 2 Evidence downgraded by 1 level because trial conducted in black South African women only and results may therefore may not be representative of population of interest.
 3 Evidence downgraded by 1 level due because 95% CI crosses 1 default MID (0.8 or 1.25).

Appendix G – Economic evidence study selection

Economic evidence for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

No evidence was identified which was applicable to this review question.

Appendix I – Health economic evidence profiles

Health economic evidence for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

No evidence was identified which was applicable to this review question.

Appendix J – Health economic analysis

Health economic analysis for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

Clinical studies

Table 11: Excluded studies

| Study | Reason for exclusion |
|--|---|
| Abbaspoor, Z., Comparison effect of vitamin C vaginal tablet with metronidazole vaginal gel treatment and relapse of bacterial vaginosis, <i>Clinical Microbiology and Infection</i> , 15 (S4), S181, 2009 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Agency for Healthcare, Research, Quality,, Screening and treatment for bacterial vaginosis in pregnancy: systematic review to update the 2001 U.S. Preventive Services Task Force recommendation, 21, 2008 | Study population not eligible - pregnant women asymptomatic for BV |
| Alsaad, A. M. S., Kaplan, Y. C., Koren, G., Exposure to fluconazole and risk of congenital malformations in the offspring: A systematic review and meta-analysis, <i>Reproductive Toxicology</i> , 52, 78-82, 2015 | Study outcomes do not meet protocol eligibility criteria - congenital malformations, heart defects, craniofacial defects, limb/musculoskeletal defects. |
| Andrews,W.W., Goldenberg,R.L., Hauth,J.C., Cliver,S.P., Copper,R., Conner,M., Interconceptional antibiotics to prevent spontaneous preterm birth: A randomized clinical trial, <i>Obstetrical and Gynecological Survey</i> , 61, 496-497, 2006 | Study does not meet protocol eligibility criteria - unclear whether women symptomatic (cultures of various microorganisms other than those of interest); combination of antibiotics not relevant to protocol. |
| Anonymous,, Do not use metronidazole to prevent delivery, <i>Pharmaceutical Journal</i> , 276, 63, 2006 | Study design does not meet protocol eligibility criteria - Opinion article. |

| Study | Reason for exclusion |
|--|---|
| Anonymous,, The management of women of reproductive age attending non-genitourinary medicine settings complaining of vaginal discharge, Journal of Family Planning and Reproductive Health Care, 32, 33-41, 2006 | Guidance - relevant references checked. |
| Bagnall, P., Rizzolo, D., Bacterial vaginosis: A practical review, JAAPA : official journal of the American Academy of Physician Assistants, 30, 15-21, 2017 | study design not eligible per protocol - narrative commentary |
| Bellad, M. B., Chalasani, P., Ganachari, M. S., Goudar, S. S., Sloan, N. L., Hoffman, M. K., Derman, R. J., Oral clindamycin to prevent preterm birth: A randomized placebo controlled trial in South India, Journal of SAFOG, 7, 191-196, 2015 | Study population does not meet protocol eligibility criteria - unclear whether women had symptomatic vaginal discharge. |
| Bellad, M. B., Hoffman, M. K., Mallapur, A. A., Charantimath, U. S., Katageri, G. M., Ganachari, M. S., Kavi, A., Ramdurg, U. Y., Bannale, S. G., Revankar, A. P., Sloan, N. L., Kodkany, B. S., Goudar, S. S., Derman, R. J., Clindamycin to reduce preterm birth in a low resource setting: a randomised placebo-controlled clinical trial, BJOG: An International Journal of Obstetrics & Gynaecology, 22, 22, 2018 | Study population does not meet protocol eligibility criteria - unclear whether women had symptomatic vaginal discharge. |
| Brocklehurst, P., Gordon, A., Heatley, E., Milan, S. J., Antibiotics for treating bacterial vaginosis in pregnancy, Cochrane Database of Systematic Reviews, 1, CD000262, 2013 | Systematic review: no additional included studies (majority of studies are in asymptomatic population) |
| Carter, T. C., Druschel, C. M., Romitti, P. A., Bell, E. M., Werler, M. M., Mitchell, A. A., National Birth Defects Prevention, Study, Antifungal drugs and the risk of selected birth defects, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 198, 191.e1-7, 2008 | Study design does not meet protocol eligibility criteria - Case control study. |

| Study | Reason for exclusion |
|--|--|
| Cruciani, F., Brigidi, P., Calanni, F., Lauro, V., Tacchi, R., Donders, G., Peters, K., Guaschino, S., Vitali, B., Efficacy of rifaximin vaginal tablets in treatment of bacterial vaginosis: A molecular characterization of the vaginal microbiota, <i>Antimicrobial agents and chemotherapy</i> , 56, 4062-4070, 2012 | Study population does not meet protocol eligibility criteria - non-pregnant women. |
| Danti, L., Gerosa, V., Rinaldo, D., Caria, M., Lupi, G., D'Oria, P., Lojacono, A., Sartori, E., Utility of a vaginal probiotic therapy in pregnancies complicated by bacterial vaginosis, <i>Reproductive Sciences</i> , 1), 127A, 2016 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Darwish,A., Elshar,E.M., Hamadeh,S.M., Makarem,M.H., Treatment options for bacterial vaginosis in patients at high risk of preterm labor and premature rupture of membranes, <i>Journal of Obstetrics and Gynaecology Research</i> , 33, 781-787, 2007 | Study design does not meet protocol eligibility criteria - Prospective cohort study. |
| Daskalakis, G. J., Karambelas, A. K., Vaginal Probiotic Administration in the Management of Preterm Premature Rupture of Membranes, <i>Fetal diagnosis and therapy</i> , 42, 92â€• 98, 2017 | Study population does not meet protocol eligibility criteria - unclear whether preterm premature rupture of membranes due to conditions of interest. |
| Daskalakis, G., Karambelas, A., Theodora, M., Antsaklis, P., Sindos, M., Asimakopoulos, G., Maritsa, V., Papantoniou, N., Antsaklis, A., Loutradis, D., Preterm premature rupture of membranes and probiotics, <i>Journal of Perinatal Medicine</i> , 45 (Supplement 2), 541, 2017 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Daskalakis, G., Karampelas, A., Gavrili, V., Papantoniou, N., Angelopoulos, P., Ntomali, A., Mesogitis, S., Probiotics for preterm premature rupture of membranes, <i>Journal of maternal fetal & neonatal medicine</i> , 27, 2014 | Study design does not meet protocol eligibility criteria - conference abstract. |

| Study | Reason for exclusion |
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| <p>Del Palacio-Hernanz, A., Sanz-Sanz, F., Rodriguez-Noriega, A., Double-blind investigation of R-42470 (terconazole cream 0.4%) and clotrimazole (cream 1%) for the topical treatment of mycotic vaginitis, <i>Chemioterapia</i> : international journal of the Mediterranean Society of Chemotherapy, 3, 192-5, 1984</p> | <p>The full-text publication of this article was unavailable</p> |
| <p>Denison, H. J., Worswick, J., Bond, C. M., Grimshaw, J. M., Mayhew, A., Gnani Ramadoss, S., Robertson, C., Schaafsma, M. E., Watson, M. C., Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush), <i>Cochrane Database of Systematic Reviews</i>, 2020</p> | <p>Does not include any pregnant women.</p> |
| <p>Di Pierro, F., Parolari, A., Brundu, B., Nigro, R., Positive clinical outcomes derived from using a proprietary mixture of selected strains during pregnancy, <i>Acta Bio-Medica de l'Ateneo Parmense</i> Acta Biomed Ateneo Parmense, 87, 259-265, 2017</p> | <p>Study population does not meet protocol eligibility criteria - proportion of women with vaginosis not clear.</p> |
| <p>Diaz-Cueto, L., Dominguez-Lopez, P., Tena-Alavez, G., Cuica-Flores, A., Rosales-Ortiz, S., Arechavaleta-Velasco, F., Effect of clindamycin treatment on vaginal inflammatory markers in pregnant women with bacterial vaginosis and a positive fetal fibronectin test, <i>International journal of gynaecology and obstetrics</i>, 107, 143-146, 2009</p> | <p>Study outcomes do not meet protocol eligibility criteria - vaginal inflammatory markers.</p> |

| Study | Reason for exclusion |
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| <p>Donders, G. G. G., Guaschino, S., Peters, K., Tacchi, R., Lauro, V., A multicenter, double-blind, randomized, placebo-controlled study of rifaximin for the treatment of bacterial vaginosis, <i>International Journal of Gynecology and Obstetrics</i>, 120, 131-136, 2013</p> | <p>Study population does not meet protocol eligibility criteria - non-pregnant women.</p> |
| <p>Donders, G. G., Zodzika, J., Rezeberga, D., Treatment of bacterial vaginosis: What we have and what we miss, <i>Expert Opinion on Pharmacotherapy</i>, 15, 645-657, 2014</p> | <p>Study design does not meet protocol eligibility criteria - Narrative review.</p> |
| <p>Donders, G., Bellen, G., Donders, F., Pinget, J., Vandeveld, I., Michiels, T., Byamughisa, J., Improvement of abnormal vaginal flora in Ugandan women by self-testing and short use of intravaginal antimicrobials, <i>European Journal of Clinical Microbiology and Infectious Diseases</i>, 36, 731-738, 2017</p> | <p>Study population does not meet protocol eligibility criteria - non-pregnant women.</p> |
| <p>Edwards, J. E., Schwartz, M. M., Schmidt, C. S., Sobel, J. D., Nyirjesy, P., Schodel, F., Marchus, E., Lizakowski, M., Demontigny, E. A., Hoeg, J., et al., A Fungal Immunotherapeutic Vaccine (NDV-3A) for Treatment of Recurrent Vulvovaginal Candidiasis-A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial, <i>Clinical infectious diseases</i>, 66, 1928-1936, 2018</p> | <p>Study intervention does not meet protocol eligibility criteria - immunotherapeutic vaccine.</p> |
| <p>Facchinetti, F., Dante, G., Pedretti, L., Resasco, P., Annessi, E., Doderò, D., The role of oral probiotic for bacterial vaginosis in pregnant women. A pilot study, <i>Minerva ginecologica</i>, 65, 215-221, 2013</p> | <p>Study does not meet protocol eligibility criteria - Non-English article.</p> |

| Study | Reason for exclusion |
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| Fredstorp, M., Jonasson, A. F., Barth, A., A new effective antibiotic-free bacterial vaginosis treatment at single-dose administration: A randomized multicenter open-label parallel-group two-part study with a novel sustained-release vaginal tablet containing oligomeric lactic acid, <i>International Journal of Gynecology and Obstetrics</i> , 5), E470, 2015 | Study design does not meet protocol eligibility criteria - conference abstract. |
| French, J.I., McGregor, J.A., Draper, D., Parker, R., McFee, J., Gestational bleeding, bacterial vaginosis, and common reproductive tract infections: risk for preterm birth and benefit of treatment, <i>Obstetrics and Gynecology</i> , 93, 715-724, 1999 | No relevant data |
| Giuffrida, G., Mangiacasale, A., Bacterial vaginosis in pregnancy: treatment with Peroxen vs vaginal Clindamycin, <i>Giornale italiano di ostetricia e ginecologia</i> , 28, 539-543, 2006 | Study does not meet protocol eligibility criteria - non-English language article. |
| Giunta, G., Giuffrida, L., Mangano, K., Fagone, P., Cianci, A., Influence of lactoferrin in preventing preterm delivery: a pilot study, <i>Molecular medicine reports</i> , 5, 162-166, 2012 | Study intervention does not meet protocol eligibility criteria - iron-binding glycoprotein (Lactoferrin). |
| Gómez, S., Agramunt, S., Checa, M. A., Carreras, R., Antibiotic treatment for prevention preterm birth in pregnant woman with bacterial vaginosis. A systematic review and a meta-analysis, <i>Journal of Maternal-Fetal & Neonatal Medicine</i> , 23, 611-612, 2010 | Systematic review includes studies of asymptomatic population |
| Gomez, S., Agramunt, S., Checa, M. A., Carreras, R., Antibiotic treatment for prevention preterm birth in pregnant woman with bacterial vaginosis. A systematic review and a meta-analysis, <i>Journal of Maternal-Fetal and Neonatal Medicine</i> , 1), 611-612, 2010 | Study design does not meet protocol eligibility criteria - conference abstract. |

| Study | Reason for exclusion |
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| Gottschick, C., Deng, Z. L., Vital, M., Masur, C., Abels, C., Pieper, D. H., Rohde, M., Mendling, W., Wagner-Dobler, I., Treatment of biofilms in bacterial vaginosis by an amphoteric tenside pessary-clinical study and microbiota analysis, <i>Microbiome</i> , 5, 119, 2017 | Study does not meet protocol eligibility criteria - healthy women (unclear whether pregnant or not); treatment comparison not relevant (amphoteric tenside versus lactic acid pessaries) for bacterial vaginosis. |
| Gülmezoglu, A. M., Azhar, M., Interventions for trichomoniasis in pregnancy, <i>Cochrane Database of Systematic Reviews</i> , 2011 | Systematic review: included studies checked for consistency. |
| Gulmezoglu, AM. , Interventions for trichomoniasis in pregnancy. , <i>Cochrane Database of Systematic Reviews</i> , No: CD000220, 2002 | Systematic review - no additional relevant studies |
| Gupta,S., Tripathi,R., Singh,N., Bhalla,P., Ramji,S., Mala,Y.M., Pregnancy outcome in asymptomatic women with abnormal vaginal flora without any treatment and after treatment with vaginal clindamycin and clotrimazole: A randomised controlled trial, <i>South African Journal of Obstetrics and Gynaecology</i> , 19, 35-38, 2013 | Study population does not meet protocol eligibility criteria - asymptomatic pregnant women. |
| Haahr, T., Jensen, J. S., Thomsen, L., Duus, L., Rygaard, K., Humaidan, P., Abnormal vaginal microbiota may be associated with poor reproductive outcomes: a prospective study in IVF patients, <i>Human reproduction (oxford, england)</i> , 31, 795â€• 803, 2016 | Study population does not meet eligibility criteria - infertile women undergoing IVF. |
| Haahr, T., Zacho, J., Brauner, M., Shathmigha, K., Skov Jensen, J., Humaidan, P., Reproductive outcome of patients undergoing in vitro fertilisation treatment and diagnosed with bacterial vaginosis or abnormal vaginal microbiota: a systematic PRISMA review and meta-analysis, <i>BJOG: An International Journal of Obstetrics & Gynaecology</i> , 22, 22, 2018 | Study population does not meet protocol eligibility criteria - infertile women undergoing IVF. |

| Study | Reason for exclusion |
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| Haji Foghaha, M., Keshavarz, T., Parsanezhad, M. E., Rajaeifard, A. R., Prevention of premature rupture of membranes and preterm labor in Shiraz, Iran, Iranian Journal of Reproductive Medicine, 1), 124, 2010 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Hantoushzadeh,S., Golshahi,F., Javadian,P., Khazardoost,S., Aram,S., Hashemi,S., Mirarmandehi,B., Borna,S., Comparative efficacy of probiotic yoghurt and clindamycin in treatment of bacterial vaginosis in pregnant women: a randomized clinical trial, Journal of Maternal-Fetal and Neonatal Medicine, 25, 1021-1024, 2012 | Study comparison does not meet protocol eligibility criteria - probiotics not a relevant comparator for bacterial vaginosis. |
| He, A., Chin, J., Lomiguen, C. M., Benefits of Probiotic Yogurt Consumption on Maternal Health and Pregnancy Outcomes: A Systematic Review, CureusCureus, 12, e9408, 2020 | This review does not include interventions for treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis or vaginal candidiasis during pregnancy |
| Holt, S., Vaginal vitamin C tablets effective for bacterial vaginosis, Focus on alternative and complementary therapies, 17, 71â€• 72, 2012 | Study intervention does not meet protocol eligibility criteria - vitamin C. |
| Jarde, A., Lewis-Mikhael, A. M., Moayyedi, P., Stearns, J. C., Collins, S. M., Beyene, J., McDonald, S. D., Pregnancy outcomes in women taking probiotics or prebiotics: a systematic review and meta-analysis, BMC Pregnancy & ChildbirthBMC Pregnancy Childbirth, 18, 14, 2018 | Study populations do not meet protocol eligibility criteria - non-infected pregnant women. |
| Joesoef, M., Schmid, G., Bacterial vaginosis, Clinical EvidenceClin Evid, 1592-600, 2002 | Study has been updated and update is available published 2005, already captured |

| Study | Reason for exclusion |
|---|--|
| Karampelas, A., Daskalakis, G., Papantoniou, N., Gavrili, V., Mesogitis, S., Angelopoulos, P., Antsaklis, A., Probiotics for preterm premature rupture of membranes, Journal of Perinatal Medicine. Conference: 11th World Congress of Perinatal Medicine, 41, 2013 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Kenyon,S., Brocklehurst,P., Jones,D., Marlow,N., Salt,A., Taylor,D., MRC ORACLE Children Study. Long term outcomes following prescription of antibiotics to pregnant women with either spontaneous preterm labour or preterm rupture of the membranes, BMC Pregnancy and Childbirth, 8, 14-, 2008 | Study population does not meet protocol eligibility criteria - PROM was not specifically due to the conditions of interest for this review. |
| Kenyon,S., Pike,K., Jones,D.R., Brocklehurst,P., Marlow,N., Salt,A., Taylor,D.J., Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial, Lancet, 372, 1310-1318, 2008 | Study population does not meet protocol eligibility criteria - unclear whether preterm rupture of the membranes due to conditions of interest. |
| Kiriara, N., Kamitomo, M., Tabira, T., Hashimoto, T., Taniguchi, H., Maeda, T., Effect of probiotics on perinatal outcome in patients at high risk of preterm birth, Journal of Obstetrics & Gynaecology ResearchJ Obstet Gynaecol Res, 44, 241-247, 2018 | Study does not meet protocol eligibility criteria - probiotics administered to women with bacterial vaginosis or constipation (proportion of women with bacterial vaginosis not reported); probiotics not relevant intervention for bacterial vaginosis. |
| Kiss, H., Petricevic, L., Husslein, P., Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery, BMJ, 329, 371, 2004 | Study population does not meet protocol eligibility criteria - asymptomatic pregnant women. |

| Study | Reason for exclusion |
|---|--|
| Kiss,H., Petricevic,L., Martina,S., Husslein,P., Reducing the rate of preterm birth through a simple antenatal screen-and-treat programme: a retrospective cohort study, <i>European Journal of Obstetrics, Gynecology, and Reproductive Biology</i> , 153, 38-42, 2010 | Study does not meet protocol eligibility criteria - pregnant women treated with standard regimens for bacterial vaginosis, candidiasis, and trichomoniasis, but outcome data not reported separately. |
| Koss, C. A., Baras, D. C., Lane, S. D., Aubry, R., Marcus, M., Markowitz, L. E., Koumans, E. H., Investigation of metronidazole use during pregnancy and adverse birth outcomes, <i>Antimicrobial Agents and Chemotherapy</i> , 56, 4800-4805, 2012 | Study does not meet protocol eligibility criteria - unclear whether symptomatic pregnant women; outcomes not reported separately for women with trichomoniasis and treated with metronidazole vs no treatment; chart review. |
| Koumans, E. H., Lane, S. D., Aubry, R., Demott, K., Webster, N., Levandowski, B. A., Berman, S., Markowitz, L. E., Evaluation of Syracuse Healthy Start's program for abnormal flora management to reduce preterm birth among pregnant women, <i>Maternal and Child Health Journal</i> , 15, 1020-1028, 2011 | Study does not meet protocol eligibility criteria - treatments included vaginal antibiotics for bacterial vaginosis/abnormal flora (RCT evidence available). |
| Krauss-silva, L., Moreira, M. E. L., Alves, M. B., Braga, A., Camacho, K. G., Batista, M. R. R., Almada-horta, A., Rebello, M. R., Guerra, F., Randomised controlled trial of probiotics for the prevention of spontaneous preterm delivery associated with bacterial vaginosis: Preliminary results, <i>Trials</i> , 239, 2011 | Study does not meet protocol eligibility criteria - women with symptomatic vaginal discharge were excluded; probiotics not a relevant intervention for bacterial vaginosis. |
| Lamont,R.F., Nhan-Chang,C.L., Sobel,J.D., Workowski,K., Conde-Agudelo,A., Romero,R., Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis, <i>American Journal of Obstetrics and Gynecology</i> , 205, 177-190, 2011 | Study population does not meet protocol eligibility criteria - asymptomatic pregnant women. |

| Study | Reason for exclusion |
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| Larsson,P.G., Fahraeus,L., Carlsson,B., Jakobsson,T., Forsum,U., Late miscarriage and preterm birth after treatment with clindamycin: A randomised consent design study according to Zelen, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 629-637, 2006 | Study population does not meet protocol eligibility criteria - asymptomatic pregnant women. |
| Larsson,P.G., Fahraeus,L., Carlsson,B., Jakobsson,T., Forsum,U., Predisposing factors for bacterial vaginosis, treatment efficacy and pregnancy outcome among term deliveries; results from a preterm delivery study, BMC Women's Health, 7, 20- , 2007 | Study population does not meet protocol eligibility criteria - unclear whether symptomatic pregnant women. |
| Laue, C., Papazova, E., Liesegang, A., Pannenbeckers, A., Arendarski, P., Linnerth, B., Domig, K. J., Kneifel, W., Petricevic, L., Schrezenmeir, J., Effect of a yoghurt drink containing Lactobacillus strains on bacterial vaginosis in women - a double-blind, randomised, controlled clinical pilot trial, Beneficial MicrobesBenef Microbes, 9, 35-50, 2018 | Study does not meet protocol eligibility criteria - pregnant women were excluded; probiotics not a relevant intervention for bacterial vaginosis. |
| Lebherz, T. B., Ford, L. C., Candida albicans vaginitis: the problem is diagnosis, the enigma is treatment, ChemotherapyChemotherapy, 28 Suppl 1, 73-9, 1982 | Study populations do not meet protocol eligibility criteria - 2 studies reported; one does not state pregnant women with symptomatic vaginal discharge; second study mainly non-pregnant women. |
| Lee,J.E., Han,J.Y., Choi,J.S., Ahn,H.K., Lee,S.W., Kim,M.H., Ryu,H.M., Yang,J.H., Nava-Ocampo,A.A., Koren,G., Pregnancy outcome after exposure to the probiotic Lactobacillus in early pregnancy, Journal of Obstetrics and Gynaecology, 32, 227-229, 2012 | Study population does not meet protocol eligibility criteria - indications for probiotics were not reported. |

| Study | Reason for exclusion |
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| Leitich,H., Brunbauer,M., Bodner-Adler,B., Kaider,A., Egarter,C., Husslein,P., Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis, American Journal of Obstetrics and Gynecology, 188, 752-758, 2003 | Systematic review includes studies of asymptomatic population |
| Mahmoudabadi,A.Z., Najafyan,M., Moghimipour,E., Alwanian,M., Seifi,Z., Lamisil versus clotrimazole in the treatment of vulvovaginal candidiasis, Iranian Journal of Microbiology, 5, 86-90, 2013 | Study population does not meet protocol eligibility criteria - Pregnant women were excluded from the study. |
| Mainini, G., Scaffa, C., First-line treatment of bacterial and mycotic vulvovaginitis with a new topical medication based on lipohydroperoxides and glycyrrhetic acid, International Journal of Gynecology and Obstetrics, 2), S255, 2009 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Mann,J.R., McDermott,S., Zhou,L., Barnes,T.L., Hardin,J., Treatment of trichomoniasis in pregnancy and preterm birth: An observational study, Journal of Women's Health, 18, 493-497, 2009 | Study population does not meet protocol eligibility criteria - unclear whether pregnant women had symptomatic vaginal discharge. |
| McDonald, H. M., O'Loughlin, J. A., Vigneswaran, R., Jolley, P. T., Harvey, J. A., Bof, A., McDonald, P. J., Metronidazole treatment of bacterial vaginosis flora and its effect on preterm birth, International journal of STD & AIDS, 8, 37-38, 1997 | not symptomatic |
| McMillan, A., Rulisa, S., Gloor, G. B., Macklaim, J. M., Sumarah, M., Reid, G., Pilot assessment of probiotics for pregnant women in Rwanda, PLoS ONE, 13, 2018 | Study does not meet protocol eligibility criteria - indications for probiotics were not reported. |

| Study | Reason for exclusion |
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| Mending, W., Caserini, M., Palmieri, R., A Randomised, controlled study to assess the efficacy and safety of nifuratel vaginal tablets on bacterial vaginosis, Sexually Transmitted Infections. Conference: STI and AIDS World Congress, 89, 2013 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Milne, L. J., Brown, A. D., Comparison of nystatin ('Nystan') and hydrargaphen ('Penotrane') in the treatment of vaginal candidosis in pregnancy, Curr Med Res Opin Current medical research and opinion, 1, 524-7, 1973 | Study population does not meet protocol eligibility criteria - unclear whether pregnant women had symptomatic vaginal discharge. |
| Mitchell, C., Balkus, J., Agnew, K., Lawler, R., Hitti, J., Changes in the vaginal microenvironment with metronidazole treatment for bacterial vaginosis in early pregnancy, Journal of Women's Health, 18, 1817-1824, 2009 | Study population does not meet protocol eligibility criteria - unclear whether women had symptomatic vaginal discharge. |
| Mitchell, C.M., Hitti, J.E., Agnew, K.J., Fredricks, D.N., Comparison of oral and vaginal metronidazole for treatment of bacterial vaginosis in pregnancy: impact on fastidious bacteria, BMC Infectious Diseases, 9, 89-, 2009 | Study population does not meet protocol eligibility criteria - asymptomatic. |
| Morales, W.J., Schorr, S., Albritton, J., Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study, American Journal of Obstetrics and Gynecology, 171, 345-347, 1994 | Population is women with history of preterm birth who will be on different treatment pathway (covered by NICE guideline NG25) |
| Morency, A. M., Bujold, E., The Effect of Second-Trimester Antibiotic Therapy on the Rate of Preterm Birth, Journal of Obstetrics and Gynaecology Canada, 29, 35-44, 2007 | Systematic review - included studies not specifically in pregnant women with conditions of interest. |
| Nct., Bacterial Vaginosis Screening and Treatment to Reduce Infective Complications, Abortion and Preterm Delivery, https://clinicaltrials.gov/show/nct00491270 , 2007 | Clinical trial record, no results posted and no related publications reported. |

| Study | Reason for exclusion |
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| Nct,, Clindamycin to Reduce Preterm Birth in a Low Resource Setting, https://clinicaltrials.gov/show/nct01800825 , 2013 | Clinical trial record - no results posted. |
| Nct,, Comparison Between Oral Clindamycin Vs Metronidazole for the Treatment of Abnormal Vaginal Flora in High Risk Pregnancies, https://clinicaltrials.gov/show/nct01722708 , 2012 | Clinical trial record, no results posted and no related publications reported. |
| Nct,, Effect of Different Courses of Lactobacilli Treatment on Bacterial Vaginosis and Pregnancy Outcomes, https://clinicaltrials.gov/show/nct01421615 , 2011 | Clinical trial record, no results posted and no related publications reported; no comparator group. |
| Nct,, Ketoconazole Gel Versus Terconazole Cream for Vaginal Candidiasis, https://clinicaltrials.gov/show/nct03473418 , 2018 | Clinical trial record, no results posted; non-English language related publication. |
| Nct,, LACTIN-V Study for Recurrent Bacterial Vaginosis, https://clinicaltrials.gov/show/nct02766023 , 2016 | Clinical trial record, no results posted and no related publications reported. |
| Nct,, Maternal Effects of Bacterial Vaginosis (BV) Treatment in Pregnancy, https://clinicaltrials.gov/show/NCT00153517 , 2005 | Study outcomes did not meet eligibility criteria - assessed BV-associated |
| Nct,, Oral Probiotics for the Treatment and Prevention of Vulvovaginal Infections in Pregnancy - Double-blind, Randomized, Placebo-controlled Study, https://clinicaltrials.gov/show/nct02795845 , 2016 | Clinical trial record, no results posted and no related publications reported. |
| Nct,, Patients With Vulvovaginal Candidiasis, https://clinicaltrials.gov/show/nct03024502 , 2017 | Clinical trial record - no results posted and no relevant publications presented. |
| Nct,, Pregnancy Complications - A Probiotic Interventional Study, https://clinicaltrials.gov/show/nct02693041 , 2016 | Study population does not meet protocol eligibility criteria - not specifically the three conditions of interest. |

| Study | Reason for exclusion |
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| Nct,, Prevention of Very Preterm Delivery by Testing for and Treatment of Bacterial Vaginosis, https://clinicaltrials.gov/show/nct00642980 , 2008 | Clinical trial record, no results posted. |
| Nct,, Probiotic for Vaginal Candidiasis in Pregnant Women, https://clinicaltrials.gov/show/NCT03940612 , 2019 | Study does not report results (clinical trial record only) (VC in pregnant women treated with probiotic vs placebo, outcomes frequency of symptoms) |
| Nct,, Probiotic Versus Placebo as Adjuvant for Bacterial Vaginosis Treatment During Pregnancy, https://clinicaltrials.gov/show/nct01558388 , 2012 | Clinical trial record, no results posted and no related publications reported. |
| Nct,, Treatment of Bacterial Vaginosis Prior to Active Labor and Infectious Morbidity, https://clinicaltrials.gov/show/NCT03954990 , 2019 | Study population does not meet eligibility criteria - women in active labour diagnosed with bacterial vaginosis (compares metronidazole vs placebo). Clinical trials record |
| Nct,, Treatment of ppROM With Erythromycin vs. Azithromycin Trial, https://clinicaltrials.gov/show/nct03060473 , 2017 | Clinical trial record, no results posted and no related publications reported. |
| Nct,, Va-Sense - Bacterial Vaginosis Once A Week Screening And Treatment To Reduce Infective Complications, Abortion And Preterm Delivery In Pregnant Women With Previous Preterm Delivery, https://clinicaltrials.gov/show/nct01152528 , 2010 | Clinical trial - single treatment arm; intervention does not meet protocol eligibility criteria. |
| Nordqvist, M., Jacobsson, B., Brantsaeter, A. L., Myhre, R., Nilsson, S., Sengpiel, V., Timing of probiotic milk consumption during pregnancy and effects on the incidence of preeclampsia and preterm delivery: A prospective observational cohort study in Norway, <i>BMJ Open</i> , 8 (1) (no pagination), 2018 | Study population does not meet protocol eligibility criteria - indication for probiotic milk consumption was not reported and women were not reported to be infected with vaginal candidiasis. |

| Study | Reason for exclusion |
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| <p>Nurbhai, M., Grimshaw, J., Watson, M., Bond, C. M., Mollison, J. A., Ludbrook, A., Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush), Cochrane Database of Systematic Reviews, 2007</p> | <p>Cochrane review - study population does not meet protocol eligibility criteria (pregnant women excluded from the review).</p> |
| <p>Nygren, P., Fu, R., Freeman, M., Bougatsos, C., Klebanoff, M., Guise, J. M., Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: An update review for the U.S. Preventive Services Task Force, Annals of Internal Medicine, 148, 220-233, 2008</p> | <p>Systematic review - study population does not meet protocol eligibility criteria (asymptomatic women).</p> |
| <p>Nyirjesy, P., Robinson, J., Mathew, L., Lev-Sagie, A., Reyes, I., Culhane, J. F., Alternative therapies in women with chronic vaginitis, Obstetrics & Gynecology, 117, 856-61, 2011</p> | <p>Study does not meet protocol eligibility criteria - not all women reported discharge and vaginal candidiasis; outcomes not reported separately in treatments of interest (all complementary and alternative medicine grouped together).</p> |
| <p>Okun, N., Gronau, K. A., Hannah, M. E., Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review, Obstetrics & Gynecology, 105, 857-68, 2005</p> | <p>Systematic review includes studies of asymptomatic population</p> |
| <p>Othman, M., Alfirevic, Z., Neilson, J. P., Probiotics for preventing preterm labour, Cochrane Database of Systematic Reviews, 2007</p> | <p>Cochrane review - included studies checked for relevance.</p> |
| <p>Ovalle, A., Romero, R., Gomez, R., Martinez, M. A., Nien, J. K., Ferrand, P., Aspillaga, C., Figueroa, J., Antibiotic administration to patients with preterm labor and intact membranes: is there a beneficial effect in patients with endocervical inflammation?, Journal of Maternal-Fetal and Neonatal Medicine, 19, 453-464, 2006</p> | <p>Study population does not meet protocol eligibility criteria - unclear whether women symptomatic for bacterial vaginosis.</p> |

| Study | Reason for exclusion |
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| Pikuza, V. V., Chilova, R. A., Ishchenko, A. I., Comparison of clinical efficacy and safety of domestic generic and original fluconazoles in the treatment of pregnant women with vulvovaginal candidiasis, Antibiotiki i khimioterapiia = antibiotics and chemotherapy [sic], 53, 35â€• 37, 2008 | Study design does not meet protocol eligibility criteria - non-English language article (Russian). |
| Qualey, J. R., Cooper, C., Monistat cream (miconazole nitrate) a new agent for the treatment of vulvovaginal candidiasis, J Reprod MedThe Journal of reproductive medicine, 15, 123-5, 1975 | Study population did not meet protocol eligibility criteria - unclear whether pregnant women had symptomatic vaginal discharge. |
| Rasti, S., Asadi, M. A., Taghriri, A., Behrashi, M., Mousavie, G., Vaginal candidiasis complications on pregnant women, Jundishapur Journal of MicrobiologyJundishapur j, 7, e10078, 2014 | Study design does not meet protocol eligibility criteria - letter to the Editor. |
| Reboucas, K. F., Eleuterio, J., Jr., Peixoto, R. C., Costa, A. P. F., Cobucci, R. N., Goncalves, A. K., Treatment of bacterial vaginosis before 28 weeks of pregnancy to reduce the incidence of preterm labor, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 146, 271-276, 2019 | Systematic review includes studies of asymptomatic population |
| Rickard, K.L., Roberts, C.L., Kotsiou, G., Morris, J.M., Treatment of asymptomatic vaginal candidiasis in pregnancy to prevent preterm birth: An openlabel pilot randomised controlled trial, Journal of Paediatrics and Child Health, 47, 10-, 2011 | Study design does not meet protocol eligibility criteria - conference abstract. |
| Roberts, C. L., Algert, C. S., Rickard, K. L., Morris, J. M., Treatment of vaginal candidiasis for the prevention of preterm birth: A systematic review and meta-analysis, Systematic Reviews, 4 (1) (no pagination), 2015 | Systematic review: included studies do not meet protocol eligibility criteria (asymptomatic pregnant women). |

| Study | Reason for exclusion |
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| <p>Roberts,C.L., Rickard,K., Kotsiou,G., Morris,J.M., Treatment of asymptomatic vaginal candidiasis in pregnancy to prevent preterm birth: an open-label pilot randomized controlled trial, BMC Pregnancy and Childbirth, 11, 18-, 2011</p> | <p>Study population does not meet protocol eligibility criteria - asymptomatic pregnant women.</p> |
| <p>Sandeford, J., Nippita, T., Morris, J., Seeho, S., The pro-pprom trial: randomised controlled trial of oral probiotic therapy for women with preterm prelabour rupture of membranes to prolong pregnancy duration, Journal of paediatrics and child health. Conference: 21st annual congress of the perinatal society of australia and new zealand, PSANZ. Australia, 53, 87, 2017</p> | <p>Study design does not meet protocol eligibility criteria - conference abstract.</p> |
| <p>Sangkomkamhang, U. S., Lumbiganon, P., Prasertcharoensuk, W., Laopaiboon, M., Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery, Cochrane Database of Systematic Reviews, 2, CD006178, 2015</p> | <p>Cochrane review - included study population does not meet protocol eligibility criteria (asymptomatic pregnant women).</p> |
| <p>Schwebke, J. R., Marrazzo, J., Beelen, A. P., Sobel, J. D., A phase 3, multicenter, randomized, double-blind, vehicle-controlled study evaluating the safety and efficacy of metronidazole vaginal gel 1.3% in the treatment of bacterial vaginosis, Sexually transmitted diseases, 42, 376-381, 2015</p> | <p>Study population does not meet protocol eligibility criteria - Pregnant women were excluded from the study.</p> |
| <p>Shennan,A., Crawshaw,S., Briley,A., Hawken,J., Seed,P., Jones,G., Poston,L., A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMETS Study, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 65-74, 2006</p> | <p>Study population does not meet protocol eligibility criteria - asymptomatic pregnant women.</p> |

| Study | Reason for exclusion |
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| Sobel, R., Sobel, J. D., Metronidazole for the treatment of vaginal infections, Expert Opinion on Pharmacotherapy, 16, 1109-1115, 2015 | Study design does not meet protocol eligibility criteria - narrative review. |
| Steele, R. W., Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis, Clinical Pediatrics, 35, 378-9, 1996 | Study design does not meet eligibility criteria - a commentary on a published article |
| Subtil, D., Brabant, G., Tilloy, E., Devos, P., Canis, F., Fruchart, A., Bissinger, M. C., Dugimont, J. C., Nolf, C., Hacot, C., Gautier, S., Chantrel, J., Jousse, M., Desseauve, D., Plennevaux, J. L., Delaeter, C., Deghilage, S., Personne, A., Joyez, E., Guinard, E., Kipnis, E., Faure, K., Grandbastien, B., Ancel, P. Y., Goffinet, F., Dessein, R., Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial, The Lancet., 2018 | Study population does not meet eligibility criteria - asymptomatic women |
| Subtil, D., Brabant, G., Tilloy, E., Salleron, J., Canis, F., Fruchart, A., Bissinger, M. C., Dugimont, J. C., Catherine, N., Chantrel, J., Jousse, M., Desseauve, D., Plennevaux, J. L., Christine, D., Deghilage, S., Personne, A., Emmanuelle, J., Dessein, R., Goffinet, F., Early clindamycin for bacterial vaginosis in low-risk pregnancy: the PREMEVA1 randomized, multicenter, double-blind, placebo-controlled trial, American Journal of Obstetrics and Gynecology, 210, S3-, 2014 | Study design does not meet protocol eligibility criteria - Conference abstract. |

| Study | Reason for exclusion |
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| <p>Sungkar,A., Purwosunu,Y., Aziz,M.F., Pratomy,H., Sutrisna,B., Sekizawa,A., Influence of early self-diagnosis and treatment of bacterial vaginosis on preterm birth rate, International Journal of Gynaecology and Obstetrics, 117, 264-267, 2012</p> | <p>Study comparison does not meet protocol eligibility criteria - comparison between test and treatment of bacterial vaginosis and usual antenatal care. There was no separate analysis of outcomes for women who received metronidazole only.</p> |
| <p>Tan, C. G., Good, C. S., Milne, L. J., Loudon, J. D., A comparative trial of six day therapy with clotrimazole and nystatin in pregnant patients with vaginal candidiasis, Postgrad Med JPostgraduate medical journal, 50 Suppl 1, 102-5, 1974</p> | <p>Study population does not meet protocol eligibility criteria - unclear whether women symptomatic vaginal discharge (candida confirmed by culture from high vaginal swab).</p> |
| <p>Thinkhamrop, J., Hofmeyr, G. J., Adetoro, O., Lumbiganon, P., Ota, E., Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity, Cochrane Database of Systematic Reviews, CD002250, 2015</p> | <p>Systematic review: included studies do not meet protocol eligibility criteria - prophylaxis antibiotics.</p> |
| <p>Turner, A. N., Carr Reese, P., Fields, K. S., Anderson, J., Ervin, M., Davis, J. A., Fichorova, R. N., Roberts, M. W., Klebanoff, M. A., Jackson, R. D., A blinded, randomized controlled trial of high-dose vitamin D supplementation to reduce recurrence of bacterial vaginosis, American Journal of Obstetrics and Gynecology, 211, 479.e1-479.e13, 2014</p> | <p>Study intervention does not meet protocol eligibility criteria - high-dose vitamin D.</p> |
| <p>Ugwumadu, A., Reid, F., Hay, P., Manyonda, I., Jeffrey, I., Oral clindamycin and histologic chorioamnionitis in women with abnormal vaginal flora, Obstetrics & GynecologyObstet Gynecol, 107, 863-8, 2006</p> | <p>Substudy of Ugwumadu 2003 RCT (which was included in Brocklehurst 2013 SR); population does not meet protocol eligibility criteria - pregnant women with asymptomatic abnormal vaginal flora.</p> |

| Study | Reason for exclusion |
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| <p>Ulbricht, Catherine, Budiman, Tantri, Chao, Wendy, Tanguay-Colucci, Shaina, Conquer, Julie, Costa, Dawn, Isaac, Richard, Parriott, Joseph, Randhawa, Amarita, Rusie, Erica, Grimes Serrano, Jill M., Varghese, Minney, Woods, Jen, Zhou, Sara, Probiotics (Bifidobacterium, Lactobacillus, and Saccharomyces boulardii): An Evidence-Based Systematic Review by the Natural Standard Research Collaboration, <i>Alternative & Complementary Therapies</i>, 17, 334-348, 2011</p> | <p>Systematic review - included studies checked (no evidence on probiotics for the treatment of vaginal candidiasis).</p> |
| <p>van Schalkwyk, J., Yudin, M. H., Allen, V., Bouchard, C., Boucher, M., Boucoiran, I., Caddy, S., Castillo, E., Kennedy, V. L., Money, D. M., Murphy, K., Ogilvie, G., Paquet, C., van Schalkwyk, J. K., Vulvovaginitis: screening for and management of trichomoniasis, vulvovaginal candidiasis, and bacterial vaginosis, <i>Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC</i>, 37, 266-276, 2015</p> | <p>Clinical practice guidelines.</p> |
| <p>Varma, R., Gupta, J. K., Antibiotic treatment of bacterial vaginosis in pregnancy: multiple meta-analyses and dilemmas in interpretation, <i>European Journal of Obstetrics, Gynecology, & Reproductive Biology</i>, 124, 10-4, 2006</p> | <p>Systematic review: included studies checked for relevancy.</p> |
| <p>Wynn, A., Ramogola-Masire, D., Gaolebale, P., Moshashane, N., Agatha Offorjebe, O., Arena, K., Klausner, J. D., Morroni, C., Acceptability and Feasibility of Sexually Transmitted Infection Testing and Treatment among Pregnant Women in Gaborone, Botswana, 2015, <i>BioMed Research International</i>, 2016 (no pagination), 2016</p> | <p>Study does not meet protocol eligibility criteria - unclear whether women were asymptomatic; outcome data not reported separately in women treated with metronidazole for vaginal trichomoniasis.</p> |

| Study | Reason for exclusion |
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| Young, G., Jewell, D., Topical treatment for vaginal candidiasis (thrush) in pregnancy, Cochrane Database of Systematic Reviews, 2001 | Cochrane review “ studies checked for eligibility: included Rubin 1980 and Ruiz-Velasco 1978, no other relevant articles. |

Economic studies

One excluded list was created for all economic studies in this guideline. See supplementary material 2 for further information.

Appendix L – Research recommendations

Research recommendations for review question: What interventions are effective in treating symptomatic vaginal discharge due to infection as a result of bacterial vaginosis, vaginal trichomoniasis, or vaginal candidiasis during pregnancy?

No research recommendations were made for this review question.