National Institute for Health and Care Excellence

FINAL

Antenatal care

[T] Management of symptomatic vaginal discharge in pregnancy

NICE guideline NG201

Evidence reviews underpinning recommendations 1.4.10 to 1.4.14

August 2021

Final

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	**Group 1 Bacterial vaginosis**
	• Vaginal antibiotics
	  ○ Clindamycin cream
	  ○ Metronidazole cream
	• Oral antibiotics
	  ○ Amoxicillin
	  ○ Clindamycin
	  ○ Metronidazole with or without erythromycin
	
	Group 2 Vaginal trichomoniasis
	• Metronidazole
	
	Group 3 Vaginal candidiasis
	• Antifungal treatment
	  ○ Any imidozole antifungal vaginal cream (for example, miconazole, clotrimazole, terconazole, econazole)
	  ○ Oral fluconazole
	  ○ Vaginal antifungal pessary (for example, nystatin, imidozole)
	• Probiotics (various strains of lactobacillus only)
	  ○ Oral
	  ▪ Food/dietary supplement
	  ▪ 'Live' yoghurt
	  ○ Vaginal
	  ▪ 'Live' yoghurt
	  ▪ Cream
	  ▪ Pessary
	  ▪ Suppository

	○ Combined oral + intravaginal
Comparison	• Any other within-group listed intervention • Placebo • No treatment
Outcome	**Critical** ○ Preterm rupture of membrane (before 37^{+0} weeks of pregnancy) ○ Preterm birth (birth before 37^{+0} weeks) **Important** ○ 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	• 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	• 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.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

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

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

Excluded studies

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

Summary of studies included in the economic evidence review

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

Economic model

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

Clinical evidence statements

Bacterial vaginosis

Comparison 1. Oral antibiotic versus placebo

Critical outcomes

Preterm rupture of membrane

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Important outcomes

Rate of cure/Symptomatic relief

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

Women's experience and satisfaction of care

No evidence was identified to inform this outcome.

Fetal death from 16 weeks of gestational age

No evidence was identified to inform this outcome.

Infant death up to 1 year chronological age

No evidence was identified to inform this outcome.

Comparison 2. Oral antibiotic versus no treatment

Critical outcomes

Preterm rupture of membrane

No evidence was identified to inform this outcome.

Preterm birth

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

Important outcomes

Rate of cure/Symptomatic relief

No evidence was identified to inform this outcome.

Women's experience and satisfaction of care

No evidence was identified to inform this outcome.

Fetal death from 16 weeks of gestational age

No evidence was identified to inform this outcome.

Infant death up to 1 year chronological age

No evidence was identified to inform this outcome.

Vaginal candidiasis

Comparison 3. Antifungal treatment versus placebo

Critical outcomes

Preterm rupture of membrane

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Important outcomes

Rate of cure/Symptomatic relief

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

Women's experience and satisfaction of care

No evidence was identified to inform this outcome.

Fetal death from 16 weeks of gestational age

No evidence was identified to inform this outcome.

Infant death up to 1 year chronological age

No evidence was identified to inform this outcome.

Comparison 4. Antifungal treatment versus probiotic

Critical outcomes

Preterm rupture of membrane

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Important outcomes

Rate of cure/Symptomatic relief

Clinical cure rate

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

Mycological cure rate

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

Women's experience and satisfaction of care

No evidence was identified to inform this outcome.

Fetal death from 16 weeks of gestational age

No evidence was identified to inform this outcome.

Infant death up to 1 year chronological age

No evidence was identified to inform this outcome.

Comparison 5. Antifungal treatment: 14 days versus 7 days

Critical outcomes

Preterm rupture of membrane

No evidence was identified to inform this outcome.

Preterm birth

No evidence was identified to inform this outcome.

Important outcomes

Rate of cure/Symptomatic relief

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

Women's experience and satisfaction of care

No evidence was identified to inform this outcome.

Fetal death from 16 weeks of gestational age

No evidence was identified to inform this outcome.

Infant death up to 1 year chronological age

No evidence was identified to inform this outcome.

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

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

The quality of the evidence

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

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

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

Benefits and harms

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

Information about vaginal discharge

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

Appropriate investigations

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

Antibiotic treatment for bacterial vaginosis

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

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

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

Antifungal treatment for vaginal candidiasis

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

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

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

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

treatment and that there was not sufficient evidence to further specify duration of antifungal treatment.

Based on the evidence that antifungal treatments were effective, the committee agreed to recommend offering imidazole to women with symptomatic vaginal discharge due to vaginal candidiasis. Since the various vaginal imidazoles examined by the studies can be assumed to have a similar mechanism of action, the committee agreed to recommend a vaginal imidazole and not a specific type of imidazole, although they recognised that not all types of imidazole are used for treating vaginal candidiasis.

Cost effectiveness and resource use

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

These recommendations reinforce current practice and there is unlikely to be any impact on resource use or costs.

References

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Ruiz-Velasco 1978

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Appendices

Appendix A – Review protocols

Table 4:Review protocol 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?

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)	Only the following listed interventions for each cause of vaginal discharge will be considered.
	
	Group 1 Bacterial vaginosis
	• Vaginal antibiotics
	  ○ Clindamycin cream
	  ○ Metronidazole cream
	• Oral antibiotics
	  ○ Amoxicillin
	  ○ Clindamycin
	  ○ Metronidazole with or without erythromycin
	
	Group 2 Vaginal trichomoniasis
	• Metronidazole
	
	Group 3 Vaginal candidiasis
	• Antifungal treatment
	  ○ Any imidozole antifungal vaginal cream (for example, miconazole, clotrimazole, terconazole, econazole)
	  ○ Oral fluconazole
	  ○ Vaginal antifungal pessary (for example, nystatin, imidozole)
	• Probiotics (various strains of lactobacillus only)
	  ○ Oral
	  ▪ Food/dietary supplement
	  ▪ 'Live' yoghurt

Field (based on PRISMA-P)	Content
	○ Vaginal ▪ 'Live' yoghurt ▪ Cream ▪ Pessary ▪ Suppository ○ Combined oral + intravaginal
Eligibility criteria – comparator(s)	• Any other intra-class intervention (such as, within-group comparison) • Placebo • No treatment Note: for the subgroup of vaginal candidiasis, the comparison of antifungal treatment combined with probiotics vs. only one of these treatments will be considered.
Outcomes and prioritisation	**Critical** ○ Preterm rupture of membrane (before 37^{+0} weeks of pregnancy) ○ Preterm birth (birth before 37^{+0} weeks) **Important** ○ 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	INCLUDE: ○ Systematic reviews ○ Randomised or quasi-randomised controlled trials (individual or cluster) If no evidence of these types is found for a listed intervention, the following types of studies in order of priority will be considered: • Non-randomised (clinical) controlled trials (individual or cluster) • Prospective comparative observational cohort studies • Retrospective comparative observational cohort studies
Other inclusion exclusion criteria	**Exclusion** POPULATION: • Multiple pregnancy • Pregnancy with known or pre-existing congenital anomalies STUDY DESIGN: • 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
	LANGUAGE: • Non-English PUBLICATION STATUS: • Conference abstract **Inclusion** COUNTRY: • No restriction
Proposed sensitivity/sub-group analysis, or meta-regression	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: • 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) Statistical heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value≥50% indicating serious heterogeneity, and ≥80% indicating very serious heterogeneity).
Selection process – duplicate screening/selection /analysis	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.
Data management (software)	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.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (for example, date, study design): • 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	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: 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. 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
Author contacts	Developer: National Guideline Alliance.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.

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	Quality assessment of individual studies will be performed using the following checklists: • 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 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/.
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.

CCTR: Cochrane Controlled Trials Register; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National 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 bias ROBIS: Risk Of Bias In Systematic reviews tool; ROBINS-I: Risk Of Bias In Non-randomized studies – of Interventions tool.

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 clotrimazol* or econazol* or imidazole* or terconazol* or nystatin* or pessar* or fluconazole* or terconazol* 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

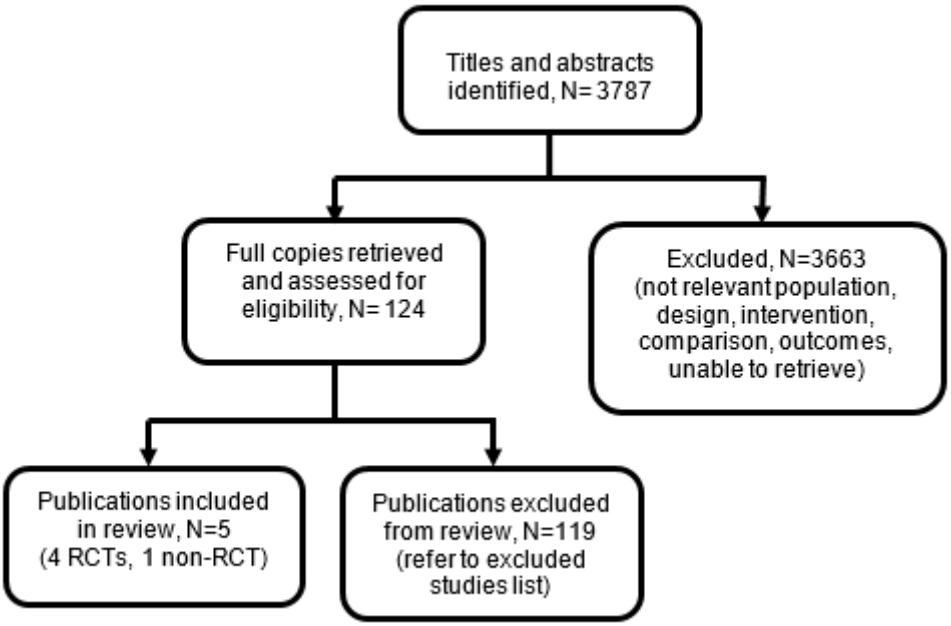
Date of last search: 3rd September 2020

#	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
Full citation 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 **Ref Id** 903908 **Country/ies where the study was carried out** Egypt **Study type** Non-randomised controlled trial **Aim of the study**	**Sample size** Intervention: N=94 (N=82 in final study group) Control: N=62 (N=47 in final study group) **Characteristics** Maternal age Intervention: 35.0, SD 3.1 Control: 34.0, SD 2.8 Parity Intervention: 3.0, SD 1.7 Control: 3.0, SD 1.3 BMI Intervention: 25.4, SD 2.1 Control: 26.2, SD 3.2 Itching before treatment - number (%) Intervention: 39 (83.0) Control: 66 (80.5) Discharge before treatment - number (%) Intervention: 35 (74.5) Control: 61 (74.4) Vulvo-vaginal redness - number (%)	**Interventions** 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.	**Details** 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. **Power analysis** To achieve 80% power, 122 participants were required. **Statistical analyses** Clinical cure rates were compared between treatment groups using the Chi-square test. Continuous outcome data were compared using the Student *t*-test.	**Results** **Important outcomes** **Rate of cure/Symptomatic relief (during pregnancy/time of symptoms)** Clinical cure rate at 1 week FU - number (%) Intervention: 34/47 (72.3) Control: 72/82 (87.8) p=0.02 Mycological cure rate at 1 week FU - number (%) Intervention: 43/47 (91.5) Control: 63/82 (76.9) p=0.01	**Limitations** **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:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess compare the effects of bee-honey and yogurt versus local antifungal agents in the treatment of vulvo-vaginal candidiasis during pregnancy. **Study dates** July 2009 to July 2011. **Source of funding** Not stated.	Intervention: 32 (68.1) Control: 53 (64.6) 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. **Inclusion criteria** • Pregnant women with vulvo-vaginal candidiasis (VVC). **Exclusion criteria** • Patients with diabetes. • Immuno-compromised patients. • Patients who refused to share or dropped out during the follow-up period.				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 **Other information** Unclear whether yogurt was 'live' nor what stain of lactobacillus.
Full citation Duff,P., Lee,M.L., Hillier,S.L., Herd,L.M., Krohn,M.A., Eschenbach,D.A., Amoxicillin treatment of bacterial vaginosis during pregnancy,	**Sample size** N=108 Intervention: N=54 (bacterial vaginosis present n=45; 9 women experienced	**Interventions** Intervention: Oral antibiotic (Amoxycillin 500 mg three times daily for 14 days)	**Details** After completion of treatment, between 34-36 weeks'gestation and at time of labour, a Gram-stained smear of vaginal fluid and	**Results** **<u>Important outcomes</u>** **Rate of cure/Symptomatic relief (during**	**Limitations** **Cochrane risk of bias tool V2:** Randomisation process: Low risk. (Adaptive randomisation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Obstetrics and Gynecology, 77, 431-435, 1991 **Ref Id** 128187 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial (RCT) **Aim of the study** To examine the effectiveness of amoxicillin for bacterial vaginosis during pregnancy. **Study dates** May 1987 to September 1988. **Source of funding** Supported by the March of Dimes grant.	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) **Characteristics** 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). **Inclusion criteria** • Pregnant women (between 15 to 25 weeks of gestation); • Diagnostic Gram stain plus positive clinical findings*. **Exclusion criteria** • Women with penicillin allergy;	Control: Placebo (three times daily for 14 days (containing lactose))	specimen was evaluated for presence of infection. **Power analysis** Not stated. **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 X^2 test or Fisher exact test. **Intention-to-treat (ITT) analysis** Outcome analysis was performed on an ITT basis.	**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)	plan using a biased-coin technique. Allocation concealed by each patient receiving an identification number and medication bottle). Deviations from intended interventions (assignment): Low risk. (Physician, study nurse, and participant blinded to medication). Missing outcome data: Some concerns. (Loss of follow-up was <20% in each group and the reasons were similar). Measurement of the outcome: Low risk. (Physician and study nurse blinded to medication). Selection of the reported result: Some concerns. (All outcomes reported, insufficient information). Other sources of bias: Low risk. (No other obvious sources of bias). Overall: Some concerns **Other information** *The diagnosis of bacterial vaginosis was assessed by Nugent criteria (7-10) and positive clinical signs (thin gray homogeneous discharge, pH

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• 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.				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** <u>**Critical outcomes**</u> **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
411196 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial. **Aim of the study** To assess the effects of metronidazole on preterm labour in the treatment of pregnant women with symptomatic bacterial vaginosis. **Study dates** March 2002 to October 2002. **Source of funding** Supported by a research grant from Deputy for Researches, Kashan University of Medical Sciences and Health Services, Iran.	Intervention: 25.7 (6.4) Control: 27.6 (5.6) Maternal weight (kg) - mean ±SD Intervention: 73 (0.1) Control: 72 (0.4) **Inclusion criteria** • 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. **Exclusion criteria** Not stated.		Not stated. **Statistical analyses** Survival analysis conducted using chi-square test and Fisher's exact tests. **Intention-to-treat (ITT) analysis**		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). Missing outcome data: Low risk. (No reported loss to follow up in either arm). Measurement of the outcome: Some concerns. (No details provided on outcome assessors, insufficient information). Selection of the reported result: Some concerns. (Protocol not available, insufficient information). Other sources of bias: Low risk. (No other obvious sources of bias) Overall: Some concerns
Full citation Rubin, A., Russell, J. M., Mauff, A., Efficacy of econazole in the treatment of candidiasis and other vaginal	**Sample size** N=67 Intervention: N=35 Control: N=32	**Interventions** Intervention: Antifungal treatment for 14 days (Econazole	**Details** Participants applied econazole for 7 days, after which one group (chosen at random) discontinued	**Results** **Important outcomes** **Rate of cure/Symptomatic relief (during**	**Limitations** **Cochrane risk of bias tool V2:** Randomisation process:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
discharges, S Afr Med JSouth African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 57, 407-8, 1980 **Ref Id** 913684 **Country/ies where the study was carried out** South Africa **Study type** Randomised trial. **Aim of the study** To assess the efficacy of econazole in the treatment of pregnant women with candidiasis and other vaginal discharges. **Study dates** February to October 1978. **Source of funding** Unclear (potential funding from Squibb Laboratories).	**Characteristics** All participants were black pregnant women. **Inclusion criteria** • Pregnant women with complaints of vaginal discharge and positive culture. **Exclusion criteria** • Pregnant women who had recently been treated with antibiotics. • Women >36 weeks' pregnancy.	vaginal cream applied at night) Control: Antifungal treatment for 7 days (Econazole vaginal cream applied for 7 days at night, then no treatment for 7 days).	treatment while a second group continued treatment for a further 7 days. **Statistical analyses** Not stated.	**pregnancy/time of symptoms)** Negative culture - number (%) Intervention: 16/31 (45.7) Control: 21/26 (65.6)	Some concerns. (No details provided, insufficient information). Deviations from intended interventions (assignment): Some concerns. (No details provided, insufficient information). Missing outcome data: Some concerns. (Loss of follow-up was <20%). 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: Some concerns. (During the 7 days of no treatment, participants in control group may have had continued effects from treatment period) Overall: High risk
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ruiz-Velasco, V., Rosas-Arceo, J., Prophylactic clotrimazole treatment to prevent mycoses contamination of the newborn, Int J Gynaecol ObstetInternational journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 16, 70-1, 1978 **Ref Id** 913685 **Country/ies where the study was carried out** Mexico **Study type** Randomised trial. **Aim of the study** To assess the effectiveness of clotrimazole treatment in pregnant women to prevent morbidity in the newborn. **Study dates** Not stated.	Intervention: N=50 Control: N=50 **Characteristics** Authors stated that both treatment groups were similar for age, weight, number of previous pregnancies and percentage of primiparae. **Inclusion criteria** • Women between 32 and 36 weeks pregnancy. • Vaginal moniliasis, confirmed by means of clinical data, fresh examinations, cytology and culture of the genital exudate. **Exclusion criteria** Not stated.	Intervention: Antifungal treatment (Clotrimazole 0.1 g vaginal tablets and vulvar cream for 6 days). Control: Placebo tablets and inert cream (for 6 days)	**Power analysis** Not stated. **Statistical analyses** Not stated. **Intention-to-treat (ITT) analysis** Not stated.	**<u>Important outcomes</u>** **Rate of cure/Symptomatic relief (during pregnancy/time of symptoms)** <u>Negative culture of vaginal exudate</u> Intervention: 44/50 (88%) Control: 29/50 (58%)	**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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not stated.					

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 amoxycillin 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)	⊕⊕⊕O 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 metronizadole (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)	⊕⊕OO 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)	⊕⊕OO 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)	⊕OOO 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)	⊕OOO 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)	⊕OOO 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, Clinical Microbiology and Infection, 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, Reproductive Toxicology, 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, Obstetrical and Gynecological Survey, 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, Pharmaceutical Journal, 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, Antimicrobial agents and chemotherapy, 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, Reproductive Sciences, 1), 127A, 2016	Study design does not meet protocol eligibility criteria - conference abstract.
Darwish,A., Elnshar,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, Journal of Obstetrics and Gynaecology Research, 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, Fetal diagnosis and therapy, 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, Journal of Perinatal Medicine, 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, Journal of maternal fetal & neonatal medicine, 27, 2014	Study design does not meet protocol eligibility criteria - conference abstract.

Study	Reason for exclusion
Del Palacio-Hernanz, A., Sanz-Sanz, F., Rodriquez-Noriega, A., Double-blind investigation of R-42470 (terconazole cream 0.4%) and clotrimazole (cream 1%) for the topical treatment of mycotic vaginitis, ChemioterapiaChemioterapia : international journal of the Mediterranean Society of Chemotherapy, 3, 192-5, 1984	The full-text publication of this article was unavailable
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 intraâ□□vaginal imidazole and triazole antiâ□□fungal treatment of uncomplicated vulvovaginal candidiasis (thrush), Cochrane Database of Systematic Reviews, 2020	Does not include any pregnant women.
Di Pierro, F., Parolari, A., Brundu, B., Nigro, R., Positive clinical outcomes derived from using a proprietary mixture of selected strains during pregnancy, Acta Bio-Medica de l Ateneo ParmenseActa Biomed Ateneo Parmense, 87, 259-265, 2017	Study population does not meet protocol eligibility criteria - proportion of women with vaginosis not clear.
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, International journal of gynaecology and obstetrics, 107, 143â□□146, 2009	Study outcomes do not meet protocol eligibility criteria - vaginal inflammatory markers.

Study	Reason for exclusion
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, International Journal of Gynecology and Obstetrics, 120, 131-136, 2013	Study population does not meet protocol eligibility criteria - non-pregnant women.
Donders, G. G., Zodzika, J., Rezeberga, D., Treatment of bacterial vaginosis: What we have and what we miss, Expert Opinion on Pharmacotherapy, 15, 645-657, 2014	Study design does not meet protocol eligibility criteria - Narrative review.
Donders, G., Bellen, G., Donders, F., Pinget, J., Vandevelde, I., Michiels, T., Byamughisa, J., Improvement of abnormal vaginal flora in Ugandan women by self-testing and short use of intravaginal antimicrobials, European Journal of Clinical Microbiology and Infectious Diseases, 36, 731-738, 2017	Study population does not meet protocol eligibility criteria - non-pregnant women.
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, Clinical infectious diseases, 66, 1928â□□1936, 2018	Study intervention does not meet protocol eligibility criteria - immunotherapeutic vaccine.
Facchinetti, F., Dante, G., Pedretti, L., Resasco, P., Annessi, E., Dodero, D., The role of oral probiotic for bacterial vaginosis in pregnant women. A pilot study, Minerva ginecologica, 65, 215â□□221, 2013	Study does not meet protocol eligibility criteria - Non-English article.

Study	Reason for exclusion
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, International Journal of Gynecology and Obstetrics, 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, Obstetrics and Gynecology, 93, 715-724, 1999	No relevant data
Giuffrida, G., Mangiacasale, A., Bacterial vaginosis in pregnancy: treatment with Peroxen vs vaginal Clindamycin, Giornale italiano di ostetricia e ginecologia, 28, 539â□□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, Molecular medicine reports, 5, 162â□□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 pretem birth in pregnant woman with bacterial vaginosis. A systematic review and a meta-analysis, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 23, 611-612, 2010	Systematic review includes studies of asymptomatic population
Gomez, S., Agramunt, S., Checa, M. A., Carreras, R., Antibiotic treatment for prevention pretem birth in pregnant woman with bacterial vaginosis. A systematic review and a meta-analysis, Journal of Maternal-Fetal and Neonatal Medicine, 1), 611-612, 2010	Study design does not meet protocol eligibility criteria - conference abstract.

Study	Reason for exclusion
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, Microbiome, 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, Cochrane Database of Systematic Reviews, 2011	Systematic review: included studies checked for consistency.
Gulmezoglu, AM. , Interventions for trichomoniasis in pregnancy. , Cochrane Database of Systematic Reviews, 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, South African Journal of Obstetrics and Gynaecology, 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, Human reproduction (oxford, england), 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, BJOG: An International Journal of Obstetrics & Gynaecology, 22, 22, 2018	Study population does not meet protocol eligibility criteria - infertile women undergoing IVF.

Study	Reason for exclusion
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.
Kirihara, 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, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 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, Antimicrobial Agents and Chemotherapy, 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, Maternal and Child Health Journal, 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, Trials, 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, American Journal of Obstetrics and Gynecology, 205, 177-190, 2011	Study population does not meet protocol eligibility criteria - asymptomatic pregnant women.

Study	Reason for exclusion
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
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, 37â□□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
Mendling, 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 OpinCurrent 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
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
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, BMJ Open, 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
Nurbhai, M., Grimshaw, J., Watson, M., Bond, C. M., Mollison, J. A., Ludbrook, A., Oral versus intraâ□□vaginal imidazole and triazole antiâ□□fungal treatment of uncomplicated vulvovaginal candidiasis (thrush), Cochrane Database of Systematic Reviews, 2007	Cochrane review - study population does not meet protocol eligibility criteria (pregnant women excluded from the review).
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	Systematic review - study population does not meet protocol eligibility criteria (asymptomatic women).
Nyirjesy, P., Robinson, J., Mathew, L., Lev-Sagie, A., Reyes, I., Culhane, J. F., Alternative therapies in women with chronic vaginitis, Obstetrics & GynecologyObstet Gynecol, 117, 856-61, 2011	Study does not meet protocol eligibility criteria - not all women reported discharge and vaginal candidiasis; outcomes not reported separately in treatments of interest (all complimentary and alternative medicine grouped together).
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	Systematic review includes studies of asymptomatic population
Othman, M., Alfirevic, Z., Neilson, J. P., Probiotics for preventing preterm labour, Cochrane Database of Systematic Reviews, 2007	Cochrane review - included studies checked for relevance.
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	Study population does not meet protocol eligibility criteria - unclear whether women symptomatic for bacterial vaginosis.

Study	Reason for exclusion
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 chemoterapy [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
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	Study population does not meet protocol eligibility criteria - asymptomatic pregnant women.
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	Study design does not meet protocol eligibility criteria - conference abstract.
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	Cochrane review - included study population does not meet protocol eligibility criteria (aymptomatic pregnant women).
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	Study population does not meet protocol eligibility criteria - Pregnant women were excluded from the study.
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 PREMET Study, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 65-74, 2006	Study population does not meet protocol eligibility criteria - asymptomatic pregnant women.

Study	Reason for exclusion
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
Sungkar,A., Purwosunu,Y., Aziz,M.F., Pratomo,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	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.
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	Study population does not meet protocol eligibility criteria - unclear whether women symptomatic vaginal discharge (candida confirmed by culture from high vaginal swab).
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	Systematic review: included studies do not meet protocol eligibility criteria - prophylaxis antibiotics.
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	Study intervention does not meet protocol eligibility criteria - high-dose vitamin D.
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	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.

Study	Reason for exclusion
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, Alternative & Complementary Therapies, 17, 334-348, 2011	Systematic review - included studies checked (no evidence on probiotics for the treatment of vaginal candidiasis).
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 Schalkwy, J. K., Vulvovaginitis: screening for and management of trichomoniasis, vulvovaginal candidiasis, and bacterial vaginosis, Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 37, 266-276, 2015	Clinical practice guidelines.
Varma, R., Gupta, J. K., Antibiotic treatment of bacterial vaginosis in pregnancy: multiple meta-analyses and dilemmas in interpretation, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 124, 10-4, 2006	Systematic review: included studies checked for relevancy.
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, BioMed Research International, 2016 (no pagination), 2016	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.

Study	Reason for exclusion
Young, G., Jewell, D., Topical treatment for vaginal candidiasis (thrush) in pregnancy, Cochrane Database of Systematic Reviews, 2001	Cochrane review â□“ 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.