Bacterial vaginosis in pregnancy and risk of spontaneous preterm delivery

Approved at the obstetrical guideline-meeting January 2015
Danish Society of Obstetrics and Gynecology (DSOG)

Update February 2019
The Lancet has now published reference 31b, by Subtil et al. (2018). The 2015 version of the DSOG guideline included this reference as a congress presentation (ref. 31a), i.e. the risk of bias was high. However, the DSOG working group finds that this publication supports the DSOG recommendations from 2015 (see "Update February 2019" for details). Apart from the "Update February 2019" paper, we did not make any other changes to the original guideline from 2015 .

Members of the working group

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Objective

The objective of this guideline is to evaluate bacterial vaginosis in pregnancy concerning

- Different treatments for prevention of preterm delivery.
- Screening of pregnant women with low as well as high risk of sPTD.
- Stratification into gestational ages below and above 16 weeks.
- Diagnostic methods.

Key words

Bacterial vaginosis, vaginal pH, pH-glove, vaginal discharge, Nugent score, Amsel score, *Gardnerella vaginalis*, *Mobiluncus species*, preterm delivery, preterm birth, GRADE, clindamycin, metronidazole, screening, treatment, probiotics, antibiotics, dysbiosis, abnormal vaginal flora.

Recommendations

Treatment with antibiotics

↓↓: We recommend against treatment of BV-positive pregnant women with antibiotics in order reducing the risk of sPTD.

- This recommendation addresses both women at low and high risk of sPTD.
- This recommendation addresses asymptomatic as well as symptomatic women (However, clindamycin might be used for treatment of symptoms).
- This recommendation addresses both treatment with metronidazole and clindamycin.
- This recommendation addresses all gestational ages of pregnancy.

Treatment with probiotics

↓?: We suggest against treatment of BV-positive pregnant women with probiotics in order reducing the risk of sPTD.

- This recommendation addresses both women at low and high risk of sPTD.
- This recommendation addresses asymptomatic as well as symptomatic women.
- This recommendation addresses all gestational ages of pregnancy.

Screening

↓↓: We recommend against screening of pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive in order reducing the risk of sPTD.

- This recommendation addresses both women at low and high risk of sPTD.
- This recommendation addresses both treatment with metronidazole, clindamycin and probiotics.

Diagnosis

↑↑: We recommend that the Nugent score constitute the gold standard.

↑↑: We recommend that properly evaluated PCR-techniques are categorized as diagnostic tools for BV, i.e. are used as conclusive alternatives to the Nugent score.

↑↑: We recommend that the Amsel criteria can be used for BV-diagnosis.

↓↓: Clinicians should not use the pH-glove for BV-diagnosis.

↑?: Clinicians might consider the pH-glove for BV-screening. When pH > 4.5, the diagnosis should be confirmed by diagnostic tool (as mentioned above, however, we recommend against screening for BV).

Table of content

Background

Bacterial vaginosis (BV) is a dysbiosis, i.e. an imbalance of the vaginal flora. Traditionally it is characterized by a replacement of *lacto bacillus spp.* into a mixed anaerobic flora including *Gardnerella vaginalis*- and *Mobiluncus*-morphotypes (1). Often, the condition is associated with vaginal discharge and fishy odor but approximately 50% are asymptomatic (2).

BV diagnosis is traditionally based on the Amsel criteria and the Nugent score. Furthermore PCR-techniques have been developed which identify pathogenic bacteria and evaluate the relative lack of *lactobacillus spp*., most of these are in accordance to the Nugent score. New microbiome studies, however, have demonstrated a greater microbial diversity with respect to former cultivation studies (3, 4) and it seems that the Nugent score and thus BV-concept need to be sub-classified (5).

Based on the Amsel criteria and the Nugent score, BV is present in about 10-20% of all Danish pregnant women (2, 6, 7). This is of obstetrical importance because BV might be associated with increased risk of spontaneous preterm delivery (sPTD), cerebral palsy, and infectious morbidity. In some populations this risk is doubled (8) but not necessarily in neither Denmark with a low sPTD-rate (6) nor in Afro-American women with a high sPTD-rate (9). In the Danish study (6), however, BV was associated with some adverse obstetric outcomes: low birth weight (OR 2.0), Preterm delivery of a low-weight infant (OR 2.5), indicated preterm delivery (OR 2.4), and chorioamnionitis (OR 2.7). Therefore, it is often discussed whether screening for BV during pregnancy is beneficial, and it is discussed whether it should be offered as a universal screening or a screening of only pregnancies with increased risk of sPTD. Some authors suggest that treatment of BV with clindamycin in early pregnancy is beneficial (5) whereas treatment after 22 weeks of gestation is not. One should, however, remember that we have only “humbling and shocking” low chance of reducing the PTD-rate in countries with low rates like Denmark and Sweden. Thus the PTD-rate was estimated to decrease from 5.9% to 5.8% if a package of several interventions (not including BV-screening) is implemented (10).

We could not identify any clinical guideline of high quality, which answers these clinically relevant questions, and we therefore decided to conduct this guideline based on the GRADE principles.

Methods

The working group intended to adhere pretty close to the GRADE principle (Grading of Recommendations Assessment); see http://www.gradeworkinggroup.org/ (11)

1. The objective was formulated.
2. Five critical and nine important outcomes were formulated.
3. Eighteen focused questions (PICO; see supplemental) considered to address the objectives were formulated.
4. A systematic literature search was conducted together with research librarians (see supplement). Two or more members of the working group independently scrutinized the search result for relevant publications.
5. Evidence was extracted from the guidelines accepted after GRADE2 evaluation.
6. Evidence was extracted from the metaanalyses and systematic reviews accepted after AMSTAR evaluation.
7. The evidence was estimated and graded.
8. The evidence was summarized and graded.
9. The recommendations were formulated and graded.
10. External reviewer were consulted.
11. Approved by the Danish Society of Obstetrics and Gynecology at the yearly obstetrical guideline meeting at January 23th, 2015?

Abbreviations

- AUC — Area under the (ROC)-curve
- BV — Bacterial vaginosis
- BW — Birth weight
- 95%CI — 95% confidence interval
- GA — Gestational age
- GRADE — Grading of Recommendations Assessment
- qPCR — Quantitative PCR (Polymerase chain reaction)
- PCR — Polymerase chain reaction
- PPROM — Preterm Prelabor Rupture of fetal Membranes
- PTD — Preterm delivery
- sPTD: — Spontaneous preterm delivery
- RR — Risk ratio

Terminology

Writer: LW

Outcomes

The outcomes were defined by the working group before the review of the literature.

- Critical outcomes: The recommendations should be based primarily on the critical outcomes.
- Important outcomes: These outcomes should be included in the recommendations especially if the critical outcomes were not addressed.

The quality of the evidence in the SOF-tables (terminology)

GRADE Working Group grading of the quality of the evidence (12):

⊕⊕⊕⊕, **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.

⊕⊕⊕⊖, **Moderate quality:** We are moderately confident in the effect of the estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖, **Low quality:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖, **Very low quality:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect

The significance of the recommendations

With the GRADE approach (13), recommendations for or against an intervention are based on the quality of evidence, the effect of intervention, size of side effect and values and preferences. When a recommendation is weak, clinicians and other health care providers need to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences.

↑↑: Strong recommendations for an intervention are made when guideline authors believe that all or almost all informed people would make the recommended choice for the given intervention.
↑?: Weak recommendations for an intervention are made when guideline authors believe that most informed people would choose the recommended course of action, but a substantial number would not.
↓?: Weak recommendations against an intervention are made when guideline authors believe that a substantial number of informed people would choose the recommended course of action, but most people would not.
↓↓: Strong recommendations against an intervention are made when guideline authors believe that all or almost all informed people would make the recommended choice against the given intervention.

High risk of sPTD - definition

- High risk pregnancies were characterized by one or more of these risk factors:
    1. Prior sPTD < 37^{+0}.
    2. Threatening PTD (tocolysis, PPROM) in prior pregnancy.
    3. Prior second trimester abortion.
- Low risk pregnancies: Pregnancies without risk these factors.

Critical outcomes

1. Perinatal morbidity
2. Long term infant morbidity (cerebral palsy, impairment, hearing impairment, cognitive disturbances, special needs in school)
3. sPTD <GA 37
4. sPTD <GA 34
5. Second trimester abortion

Important outcomes

6. Infant mortality
7. Birth weight
8. Side-effects sufficient to stop or change treatment
9. PPROM
10. Fever during labor or delivery
11. Incidence of chorioamnionitis treated with antibiotics
12. Incidence of postpartum fever
13. Incidence of postpartum uterine infection
14. Admission to neonatal unit

Stakeholder involvement

Writer: NU

- **DSOG (Danish collaboration of obstetrics and gynecology):** The obstetricians within this group were all appointed according to the tradition of the DSOG-guideline organization (Sandbjerg meetings).
- **General practitioners**: As the working group did not recommend screening by the general practitioners, they were not involved.

- **Patients**: The working group did not find it relevant to involve patient organizations.
- **Hospital owners**: As the recommendations did not cause logistic, economic or educational implications, the hospital owners were not involved.
- **Midwifes**: We did not ask the Danish Association of Midwifes to appoint members of the working group but one midwife applied for participation herself.

ICD-10

DO988 (Bacterial infection in pregnancy) + N768C (bacterial vaginosis)
Not among the ICD-10 codes recommended by DSOG.

Question 1: Low risk, screening, < 16 weeks, probiotics

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with probiotics reduce the risk of sPTD?

Writer: RBH

Recommendation

↓↓: We recommend against screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with probiotics to reduce the risk of sPTD.

Background

The guideline-group did consider the possible association between probiotics (see page 97) in food and reduced risk of sPTD of relevance of this guideline. Thus, the 950 cases and the 17,938 controls in the Norwegian Mother and Child Cohort (14) answered a food-frequency questionnaire showing that the intake of milk-based products containing probiotic lactobacilli was associated with a reduced risk of sPTD ($OR_{adjusted}$: 0.86; 95%CI 0.74-0.99).

Literature

We could not identify studies on this question.

Considerations concerning question 1	
Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of cases with probiotics reduce the risk of sPTD?	
Quality of the evidence	Neither critical nor important outcomes were addressed in RCT. Concerning the cohort study (14), the quality score according to GRADE is very low.
Balance between pro et con	The risk of sPTD < 37 weeks might be reduced by 14% (14). We consider this reduction to be of clinical relevance. We found no evidence that the intervention is associated with negative obstetric outcomes. We found no indications that the intervention is harmful (see page 97).
Values and preferences	Even though screening can induce anxiety and unnecessary treatment, we assume that most women will prefer this intervention if it reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer probiotics to antibiotics if the effects are similar.
Other consideration	Most probably, clindamycin is more effective than metronidazole and probiotics (See question 7, 8 and 9). However, from a microbiological perspective, we are worried about a widespread use of clindamycin in women at low risk of sPTD (see page 94). We do not expect the intervention to be cost-effective and fear that the necessary resources may be taken from the other important aspects of the antenatal care. However, sPTD has serious psychological, health and economic consequences (15-18).

Rationale for the recommendation (question 1)

The quality of the evidence is very low, the resources needed for the intervention are relatively demanding, and the possible psychological impact on the pregnant women is of concern.

Question 2: low risk, screening, < 16 weeks, metronidazole

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with metronidazole reduce the risk of sPTD?

Writer: LW

Recommendation

↓↓: We recommend against screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with metronidazole to reduce the risk of sPTD.

Background

The guideline-group did consider a possible treatment effect of metronidazole on reducing the rate of sPTD as relevant for this guideline.

In a small RCT from 1994 (19), pregnant women with BV at a GA of 13 - 20 weeks and a history of sPTD, metronidazole reduced the risk of repeat sPTD.

Literature

Only one study included (page 46).

Summary of Findings – question 2

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of cases with metronidazole reduce the risk of sPTD?

Population: Pregnant women with gestational age < 16 weeks
Intervention: Screening for BV and treatment og BV-positive cases with metronidazole
Control group: No screening for BV

Outcome	**Absolut effect* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of evidence (GRADE)**	**Comments**
	Control	**Intervention**				
	N per 1000	**N per 1000**				
Critical outcomes						
sPTD < GA 37^{+0}	52	34 (12-96)	0.66 (0.23-1.86)	331 (1 study)	⊕⊖⊖⊖* **very low**	Ref: (20)

*Background for evaluation of evidence: 1) The risk of bias was moderate (see page 46); 2) We could not evaluate the inconsistency as only one study was included. This is considered to be a serious limitation; 3) The indirectness was high as the study is based on a self-test with pH in Jakarta; 4) The risk of imprecision was moderate as the confidence interval was broad, 5) The risk of publication bias was high as only one very small study was included.

Considerations concerning question 2

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of cases with metronidazole reduce the risk of sPTD?	
Quality of the evidence	Only one critical outcome and no important outcomes were addressed. The quality of the evidence concerning this outcome single is very low.
Balance between pro et con	The risk of sPTD < 37 weeks might be reduced by 34% which we consider of clinical relevance. We found no evidence that the intervention is associated with negative obstetric outcomes. We found no evidence that the intervention is harmful (see page 97).
Values and preferences	Even though screening can induce anxiety and unnecessary treatment, we assume that most women will prefer this intervention if it reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer probiotics to antibiotics if the effects are similar.
Other consideration	Most probably, clindamycin is more effective than metronidazole and probiotics (See question 7, 8 and 9). However, from a microbiological perspective, we are worried about a widespread use of clindamycin in women at low risk of sPTD (see page 94). The microbiological concerns of widespread use of metronidazole are limited (see page 97). We do not expect the intervention to be cost-effective and fear that the necessary resources may be taken from the other important aspects of the antenatal care. However, sPTD has serious psychological, health and economic consequences (15-18).

Rationale for the recommendation (question 2)

The quality of the evidence is very low, the resources needed for the intervention are relatively demanding, and the possible psychological impact on the pregnant women is of concern.

Question 3: Low risk, screening GA < 16 weeks, clindamycin

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with clindamycin reduce the risk of sPTD?

Writer: LW

Recommendation

↓↓: We recommend against screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with clindamycin to reduce the risk of sPTD.

Background

Clindamycin is effective for the treatment of BV. In regards of prevention of sPTD it has been suggested that the effect depends on the population screened and treated and on the timing of treatment (21).

Literature

Only one study was included (page 46).

Summary of Findings-table – question 3

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of cases with clindamycin reduce the risk of sPTD?

Population: Low risk women.
Intervention: Screening for BV and treatment of cases with clindamycin.
Control group: Usual care without screening for BV.

Outcome	**Absolut effect* (95% CI)**		**Relative effect** (95% CI)	**Number of participants** (studies)	**Quality of evidence** (GRADE)	**Comments**
	Control (n/1000)	**Clindamycin** (n/1000)				
Critical outcomes						
sPTD < GA 37^{+0}	49	30 (22-42)	0.75 (0.61-0.94)	3564 (1 study)	⊕⊕⊖⊖ low*	Ref: (22)

*Background for evaluation of evidence: 1) The risk of bias was moderate as the results are based on a subanalysis conducted by this guideline-group (See page 46); 2) We could not evaluate the inconsistency as only one study was included. This is considered to be a moderate limitation; 3) The indirectness was moderate as the inclusion criteria was GA < 20^{+0} weeks not 16^{+0} weeks; 4) The risk of imprecision was relatively low as the CI did not include figures that would change out conclusion; 5) The risk of publication bias was high as only one study was included. The study, however, was large.

Considerations concerning question 3

Does screening of low risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of cases with clindamycin reduce the risk of sPTD?

Quality of the evi- dence	Only one critical outcome and no important outcomes were addressed. The quality of the evidence concerning this single outcome is low.
Balance between pro et con	The risk of sPTD < 37^{+0} weeks might be reduced by 25% which we consider of clinical relevance. We found no evidence that the intervention is associated with negative obstetric outcomes. The intervention is associated with some adverse effects (see page 94).
Values and preferences	Even though screening can induce anxiety and unnecessary treatment, we assume that most women will prefer this intervention if it reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer probiotics to antibiotics if the effects are similar.
Other consideration	Concerning the outcome sPTD < 32^{+0} weeks, the study found no effect of screening and treatment or BV, candidiasis and trichomoniasis (22). Because of lack of data in the publication, it was not possible to do a sub-analysis stratifying for BV on this critical outcome. Concerning treatment of BV positive pregnant women with clindamycin, we suggest that this intervention should not be used (See question 9, page **Fejl! Bogmærke er ikke defineret.**). We are worried about the microbiological concerns against widespread use of clindamycin (see page 94). The teratogenic concerns by treatment with clindamycin are limited (see page 93). We do not expect the intervention to be cost-effective and fear that the necessary resources may be taken from the other important aspects of the antenatal care. However, sPTD has serious psychological, health and economic consequences (15-18).

Rationale for the recommendation (question 3)

The quality of the evidence is low, the resources needed for the intervention are relatively demanding, and the possible psychological impact on the pregnant women is of concern. Furthermore, we suggest that BV-positive pregnant women regardless of risk status should not be treated with clindamycin in order to reduce the risk of sPTD (question 9, 11 and 14; page 23, 29, and 33).

Question 4: High risk, screening, < 16 weeks, probiotics

Does screening of high risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with probiotics reduce the risk of sPTD?

Writer: RBH

Recommendation

↓↓: We recommend against screening of high risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with probiotics to reduce the risk of sPTD.

Background

The guideline-group did consider the possible association between probiotics in food and reduced risk of sPTD of relevance of this guideline (see question 1, page 9).

Literature

We could not identify any RCT on this question. The cohort study (14) which was of very low quality included pregnant women at low risk of sPTD.

Considerations concerning question 4	
Does screening of high risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of cases with probiotics reduce the risk of sPTD	
Quality of the evidence	Neither critical nor important outcomes were addressed in RCT. Concerning the cohort study (14), the quality score according to GRADE is very low.
Balance between pro et con	The risk of sPTD < 37 weeks might be reduced by 14% (14). We consider this reduction to be of clinical relevance. We found no evidence that the intervention is associated with negative obstetric outcomes. We found no indications that the intervention is harmful (see page 97).
Values and preferences	Even though screening can induce anxiety and unnecessary treatment, we assume that most women at high risk of sPTD will prefer this intervention if it reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer probiotics to antibiotics if the effects are similar.
Other consideration	The indirect evidence in favor of this intervention is very weak. We found no evidence on cost-effectiveness of the intervention. Most probably, clindamycin is more effective than metronidazole and probiotics (See question 7, 8 and 9).

Rationale for the recommendation (question 4)

The quality of the evidence is low, but the resources needed for the intervention are not demanding. Instead of screening for BV a recommendation of probiotics to these women could be considered.

Question 5: high risk, screening, < 16 weeks, metronidazole

Does screening before GA < 16^{+0} for BV and treatment metronidazole in high risk pregnant women reduce the risk of sPTD?
Writer: LW

Recommendation

↓↓: We recommend against screening of high risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with metronidazole to reduce the risk of sPTD.

Background

The guideline-group did consider a possible treatment effect of metronidazole on reducing the rate of sPTD as relevant for this guideline.
In a small RCT from 1994 (19), pregnant women with BV at a GA of 13 - 20 weeks and a history of sPTD, metronidazole reduced the risk of repeat sPTD.

Literature

We could not identify RCTs on this question. The indirect evidence for this intervention is very weak (19) and was therefore not taken into consideration.

Considerations concerning question 5	
Does screening before GA < 16^{+0} for BV and treatment metronidazole in high risk pregnant women reduce the risk of PTD?	
Quality of the evidence	Neither critical nor important outcomes were addressed
Balance between pro et con	We found no evidence that the intervention is associated with negative obstetric outcomes. We found no evidence that the intervention is harmful (see page 115).
Values and preferences	Not relevant as no pros were identified
Other consideration	Metronidazole-treatment of BV-positive women at any GA and high risk of sPTD might reduce the risk of repeat sPTD by 9% (se question 13 page) which we do not consider of clinical relevance. The microbiological concerns of widespread use of metronidazole are limited (see page 97). Most probably, clindamycin is more effective than metronidazole at all gestational ages. However, from a microbiological perspective, we are worried about a widespread use of clindamycin in women at low risk of sPTD (see page 94).

Rationale for the recommendation (question 5)

We did not find any direct evidence in favour of this intervention.
As we suggest that pregnant women with BV should not be treated with metronidazole in order to reduce the risk of sPTD (See question 8, 10 and 13), we recommend against screening for this condition.

Question 6: High risk, screening, <16 weeks, clindamycin

Does screening before GA < 16^{+0} for BV and treatment with clindamycin in high risk pregnant women reduce the risk of sPTD?
Writer: LW

Recommendation

↓↓: We recommend against screening of high risk pregnant women for BV before a GA of 16^{+0} weeks and treatment of screen-positive with clindamycin to reduce the risk of sPTD.

Background

Clindamycin is effective for the treatment of BV. In regards of prevention of sPTD it has been suggested that the effect depends on the population screened and treated and on the timing of treatment (21).

Literature

We could not identify any RCT addressing this question.

Considerations concerning question 6	
Does screening before GA < 16^{+0} for BV and treatment with clindamycin in high risk pregnant women reduce the risk of PTD?	
Quality of the evidence	This question was not address directly in any RCT.
Balance between pro et con	Not addressed
Values and preferences	Screening can induce anxiety and unnecessary treatment. We assume that most Danish women have a dislike toward antibiotics.
Other consideration	We are worried about the microbiological concerns against widespread use of clindamycin (see page 112). The teratogenic concerns by treatment with clindamycin are limited (see page 109). Though, sPTD has serious psychological, health and economic consequences (15-18). We found no evidence on cost-effectiveness of the intervention. sPTD has serious psychological, health and economic consequences (15-18, 23).

Rationale for the recommendation (question 6)

As we suggest that pregnant women at high risk of sPTD with BV should not be treated with clindamycin in order to reduce the risk of sPTD (See question 9, 11 and 14), we cannot recommend screening for this condition.

Question 7: Low risk, treatment, any GA, probiotics

Does treatment with probiotics of low risk pregnant women with BV at any GA reduce the risk of sPTD?
Writer: RBH

Recommendation

↓?: We suggest against treatment of low risk pregnant women for BV at any GA with probiotics to reduce the risk of sPTD.

Background

The guideline-group did consider the possible association between probiotics in food and reduced risk of sPTD of relevance of this Guideline (See question 1 at page 9).

Literature

We only identified one RCT on the subject (page 47).

Summary of Findings– question 7						
Does treatment with probiotics of low risk pregnant women with BV at any GA reduce the risk of sPTD?						
Population: Low risk with BV at any GA **Intervention:** Treatment with probiotics. **Control group:** No treatment.						
Outcome	**Absolut effect* (95% CI)**		**Relative effect** (95% CI)	**Number of participants** (studies)	**Quality of evidence** (GRADE)	**Comments**
	Control (n/1000)	**Intervention** (n/1000)				
Critical outcomes						
sPTD < GA 37^{+00}	33	17 (6-48)		605 (1 study)	very low ⊕⊖⊖⊖	Ref: (24)
sPTD < GA 34^{+0}	10	3 (0-32)		605 (1 study)	very low ⊕⊖⊖⊖	Ref: (24)
Important outcomes						
Infant mortality					very low ⊕⊖⊖⊖	One of 301 in the control group. None of 304 in the intervention group. (24)
*Background for evaluation of evidence: 1) The risk of bias was moderate; 2) The inconsistency could not be evaluated as only one small study was included. This is considered to be a serious limitation; 3) Indirectness was a limitation as the population was from Brazil and only those with pH > 4.5 had a Nugent score.; 4) The imprecision was high as the confidence interval was broad; 5) The risk of publication bias was very high as only one relatively small study was included.						

Considerations concerning question 7
Does treatment with probiotics of low risk pregnant women with BV at any GA reduce the risk of sPTD?

Quality of the evi- dence	Only two critical and one important outcome were addressed. The quality of the evidence was very low.
Balance between pro et con	The risk of sPTD < 37 weeks might be reduced by 50%. We consider this reduction to be of clinical relevance. We found no evidence that the intervention is associated with negative obstetric outcomes. We found no indications that the intervention is harmful (see page 97).
Values and preferences	We assume that most patients will prefer an effective treatment. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar. sPTD has serious psychological, health and economic consequences.
Other consideration	The indirect evidence for this intervention is very weak. Most probably clindamycin is more effective (se question 3, 9, 11, 14, and 17)

Rationale for the recommendation (question 7)

As the quality of the evidence is very low, we do not think probiotics can be classified as effective. On the other hand we did not find evidence that the intervention is harmful. We therefore assume that some women request this "ecologic" intervention as we recommend that these women should not be treated with neither metronidazole (question 8, page 21) nor clindamycin (question 9, page 23).

Question 8: Low risk, treatment, any GA, metronidazole

Does metronidazole treatment of low risk pregnant women with BV at any GA reduce the risk of sPTD?
Writer: JS

Recommendation

↓↓ We recommend against treatment of low risk pregnant women for BV at any GA with metronidazole to reduce the risk of sPTD.

Background

BV has been associated with sPTD and metronidazole has been use for treatment of BV in non-pregnant women. Due to increase focus at these associations a number of pregnant women might be diagnosed with BV even though they are not at increased risk of sPTD.

Literature

Five studies were included (page 48) of which two included women with and without previous sPTD (25).

Summary of Findings – question 8						
Does metronidazole treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?						
Population: Low risk at any GA with BV **Intervention:** Metronidazole **Control group:** No treatment						
Outcome	**Absolut effect* (95% CI)**		**Relative effect** (95% CI)	**Number of participants** (studies)	**Quality of evidence** (GRADE)	**Comments**
	Control (n/1000)	**Intervention** (n/1000)				
Critical outcomes						
sPTD < GA 37^{+0}	113	126 (104-152)	1.10 (0.91-1.33)	3271 (5 studies)	⊕⊕⊖⊖ low*	Ref: (25, 26, 26-29)
sPTD < GA 34^{+0}	30	30 (20-44)	1.00 (0.67-1.49)	3151 (4 studies)	⊕⊕⊖⊖ low**	Ref: (25, 26, 26-29)
Important outcomes						
Perinatal mortality	24	15 (1-163)	0.62 (0.06-6.70)	148 (1 study)	⊕⊖⊖⊖ very low***	Ref. (28)
Birth weight < 2500 g < 1500 g	113 27	108 (83-139) 20 (11-36)	0.96 (0.74-1.23) 0.74 (0.41-1.33)	1919 (1 study) 1919 (1 study)	⊕⊖⊖⊖ very low****	Ref. (26)

Side effects sufficient to stop or change treatment	91	216 (171-273)	2.37 (1.88-3.00)	1919 (1 study)	⊕⊖⊖⊖ very low****	Ref. (26)
PPROM	33	28 (13-60)	0.86 (0.40-1.83)	857 (1 study)	⊕⊖⊖⊖ very low****	Ref. (30)

*Background for evaluation of evidence: 1) The risk of bias is low; 2) The inconsistency is moderate with an I^2 of 48%; 3) two studies included women with and without previous PTD; 4) The risk of imprecision was moderate as the 95%CI included clinically relevant figures; 5) The risk of publication bias was moderate according to the Funnel-plot

** Background for evaluation of evidence: 1) The risk of bias is low; 2) The inconsistency is moderate with an I^2 of 0%; 3) The indirectness was affected a little as some studies used GA < 32^{+0} weeks as outcome instead of GA<34^{+0} weeks, two studies included women with and without previous PTD (does that mean a normal population or a selected population?); 4) The risk of imprecision was moderate as the 95%CI included clinically relevant figures; 5) The risk of publication bias was moderate according to the Funnel-plot

*** Background for evaluation of evidence: 1) The risk of bias is low; 2) The inconsistency could not be assessed as only one study was included 3) The indirectness was very low; 4) The risk of imprecision was very high; 5) The risk of publication bias was very high as only one study was included

**** Background for evaluation of evidence: 1) The risk of bias is low; 2) The inconsistency could not be assessed as only one study was included 3) The indirectness was very low; 4) The risk of imprecision was moderate as the 95%CI included clinically relevant figures; 5) The risk of publication bias was very high as only one study was included.

Considerations concerning question 8	
Does metronidazole treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?	
Quality of the evidence	Only two critical outcomes were addressed of which the Quality of evidence (GRADE) was low. Four important outcomes were addressed of which the quality of evidence (GRADE) was very low
Balance between pro et con	We found no evidence that the intervention is effective concerning the two critical outcomes addressed. We found some evidence that the intervention might improve the rate of important outcomes. We found some evidence that more about 10% of the treated women interrupted the metronidazol-treatment because of side effect. We found no evidence that the intervention is harmful.
Values and preferences	We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Clindamycin is probably better than metronidazole

Rationale for the recommendation (question 8)

We have no evidence that the intervention is effective.

Question 9: Low risk, treatment, any GA, clindamycin

Does clindamycin treatment of low risk pregnant women with BV at any GA reduce the risk of sPTD?
Writer: JS & LH

Recommendation

↓↓: We recommend against treatment of low risk pregnant women for BV at any GA with clindamycin to reduce the risk of sPTD.

Background

BV has been associated with sPTD and clindamycin has been use for treatment of BV in non-pregnant women. Due to an increased focus at these associations a number of pregnant women might be diagnosed with BV even though they are not at increased risk of sPTD.

Literature

Ten studies were included (page 52). One study has only been published as an abstract (31). Additional data obtained from an oral presentation of that study.

Summary of Findings-table – question 9						
Does clindamycin treatment of low risk pregnant women with BV at any GA reduce the risk of PTD?						
Population: Pregnant women with BV at any gestational age **Intervention:** Treatment for BV and treatment og BV-positive cases with clindamycin. **Control group:** no screening for BV						
Outcome	**Absolut effect* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of evidence (GRADE)**	**Comments**
	Control	**Clindamycin**				
Critical outcomes						
sPTD < GA 37^{+0}	82	71 (60-86)	0.87 (0.73-1.05)	6392 (10 studies)	⊕⊕⊖⊖ low*	Ref: (22, 31-39)
Subanalysis *sPTD < GA 37^{+0}* *GA < 20^{+0} weeks*	*52*	*49* *(37-63)*	*0.94* *(0.72-1.23)*	*4755* *(5 studies)*	*⊕⊕⊖⊖ low***	*Ref:* (22, 31, 33-35) *This subanalysis included only studies based on intervention < 20^{+0} weeks*
Subanalysis: *sPTD < GA 37^{+0}* *without ref* (31)	*104*	*82* *(67-101)*	*0.79* *(0.64-0.97)*	*3532* *(9 studies)*	⊕⊕⊖⊖ low***	*Ref:* (22, 32-39) *This subanalysis did not include data from the reference* (31) *which has not been published in a peer reviewed journal*
Subanalysis: *sPTD < GA 37^{+0}* *GA < 20^{+0} weeks* *(without ref* (31)*)*	*63*	*46* *(31-68)*	*0.73* *(0.50-1.08)*	*1895* *(4 studies)*	⊕⊕⊖⊖ low****	*Ref:* (22, 34, 35, 40) *This subanalysis included only studies based on intervention < 20^{+0} weeks and did not include data from reference* (31) *which has not been published in a peer reviewed journal*
sPTD < GA 34^{+0}	18	19 (11-31)	1.02 (0.62-1.68)	4568 (4 studies)	⊕⊕⊖⊖ low¤	Ref: (22, 31-39)
sPTD < GA 34^{+0} *Subanalysis* GA < 20^{+0} weeks	11	10 (2-21)	0.92 (0.45-1.85)	3645 (2 studies)	*⊕⊕⊖⊖ low* ¤¤*	Ref: (31, 35) *This subanalysis included only studies based on intervention < 20^{+0} weeks*
sPTD < GA 34^{+0} *Subanalysis: without ref* (31)	*27*	*26* *13-50)*	*0.95* *(0.49-1.87)*	*1708* *(3 studies)*	*⊕⊕⊖⊖ low¤¤¤*	*Ref:* (22, 32-39) *This subanalysis did not include reference* (31)
Subanalysis:	*13*	*3* *(0-22)*	*0.20* *(0.02-1.68)*	*785* *(1 study)*	*⊕⊖⊖⊖ very low ¤¤¤*	*Ref:* (35) *This subanalysis included only studies based on intervention < 20^{+0} weeks and did not include reference* (31)

sPTD < GA 34^{+0} GA < 20^{+0} weeks (without ref (31)*)*						
Late miscarriage	63	34 (16-68)	0.53 (0.26-1.08)	727 (2 studies)	⊕⊖⊖⊖ very low†	Ref: (31, 32)
Important outcomes:						
PPROM	87	100 (48-211)	1.15 (0.55-2.43)	342 (2 studies)	⊕⊖⊖⊖ very low††	Ref: (32, 37)
Post partum fever	123	76 (44-131)	0.62 (0.36-1.07)		⊕⊖⊖⊖ very low††	Ref: (32, 33, 37)
Side effects	26	38 (20-74)	1,49 (0.78-2.86)	1555 (2 studies)	⊕⊖⊖⊖ very low††	Ref: (36, 38, 41),
NICU admission	64	46 (30-70)	0.71 (0.46-1.09)	1351 (3 studies)	⊕⊖⊖⊖ very low††	Ref: (36, 37, 41)
BW < 2500 g	94	88 (61-128)	0.94 (0.65-1.36)	1160 (3 studies)	⊕⊖⊖⊖ very low††	Ref: (36, 38, 41)
Perinatal mortality	3/201	1/208		calculate	⊕⊖⊖⊖ very low††	Ref: (34)

*Background for evaluation of evidence: 1) The risk of bias was high as not all data in reference (31) are published; 2) the inconsistency was moderate with an I^2 = 54%; 3) The indirectness was moderate as one study (32) included treatment for yeast, two studies used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was high as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was low according to the Funnel-plot.

** Background for evaluation of evidence: 1) The risk of bias was high as not all data in reference (31) are published; 2) the inconsistency was moderate with an I^2 = 41%; 3) The indirectness was moderate as two studies used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was high as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was moderate as only 3 studies were included.

*** Background for evaluation of evidence: 1) The risk of bias was low; 2) the inconsistency was moderate with an I^2 = 47%; 3) The indirectness was moderate as two studies used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was moderate as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was low according to the Funnel-plot.

**** Background for evaluation of evidence: 1) The risk of bias was low; 2) the inconsistency was low with an I^2 = 20%; 3) The indirectness was moderate as one study used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was high as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was moderate as only few studies were included.

¤ Background for evaluation of evidence: 1) The risk of bias was high as not all data in reference (31) are published;; 2) the inconsistency was moderate with an I^2 = 62%; 3) The indirectness was moderate as one studie used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most

studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was moderate as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was moderate according to the Funnel-plot.

¤¤ Background for evaluation of evidence: 1) The risk of bias was low; 2) the inconsistency could not be evaluated as only one study was included; 3) The indirectness was moderate as the study used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria; 4) The risk of imprecision was very high; 5) The risk of publication bias was high as only one study was included.

¤¤¤ Background for evaluation of evidence: 1) The risk of bias was high as not all data in reference (31) are published; 2) the inconsistency was moderate with an $I^2 = 55\%$; 3) The indirectness was moderate as one study used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria and both studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was high as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was moderate as only 2 studies were included.

† Background for evaluation of evidence: 1) The risk of bias low; 2) the inconsistency was moderate with an $I^2 = 53\%$; 3) The indirectness was moderate as two studies used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was moderate as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was high as only two small studies were included

††Background for evaluation of evidence: 1) The risk of bias low; 2) the inconsistency was moderate with an $I^2 > 40\%$; 3) The indirectness was moderate as two studies used "abnormal flora" (Nugent-score 4-10) as diagnostic criteria (34, 36) and most studies used any PTD as outcome instead of sPTD; 4) The risk of imprecision was moderate as the 95%CI included figures which might lead to other conclusions; 5) The risk of publication bias was high as only two few studies were included

Considerations concerning question 9	
Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?	
Quality of the evidence	Two of five critical outcomes were addressed with low quality of evidence, one with very low quality of evidence. Six important outcomes were addressed with very low quality of evidence.
Balance between pro et con	sPTD $<37^{+0}$ weeks was reduced by 13%, whereas sPTD $<34^{+0}$ weeks was increased by 4%. We found no evidence that the intervention should be harmful.
Values and preferences	We assume that most women at high risk of sPTD are motivated for an intervention that may reduce their risks of sPTD.
Other consideration	The available information from the unpublished study by Subtil et al. (31) seems to be trustworthy. Even though the subanalysis with did not include these results indicated that the intervention might be more beneficial, we therefore decided to base our recommendations primarily on the analysis with include data from Subtil et al (31). We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.

Rationale for the recommendation (question 9)

The members of the guideline group were very ambiguous concerning this recommendation. We decided, however, to base the recommendation primarily on the estimated risks of sPTD $< 37^{+0}$ weeks and sPTD $< 34^{+0}$ weeks.

Question 10: high risk, treatment, any GA, metronidazole

Does metronidazole treatment of high risk pregnant women with BV and at any GA reduce the risk of sPTD?
Writer: JS

Recommendation

↓↓: We recommend against treatment of high risk pregnant women for BV at any GA with metronidazole to reduce the risk of sPTD.

Background

BV has been associated with sPTD and metronidazole has been use for treatment of BV in non-pregnant women. Due to an increased focus at these associations a number of pregnant women a high risk of sPTD might be diagnosed with BV.

Literature

Six RCT were included (page 63).

Summary of Findings-table – question 10

Does metronidazole treatment of high risk pregnant women with BV and at any GA reduce the risk of PTD?

Population: pregnant women with BV at any GA
Intervention: metronidazole
Control group: no treatment

Outcome	**Absolut effect* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of evidence (GRADE)**	**Comments**
	Control	**Metronidazole**				
Critical outcomes						
sPTD < GA 37^{+0}	334	308 (251-381)	0.92 (0.75-1.14)	681 (6 studies)	⊕⊕⊖⊖ low*	Ref: (19, 25, 26, 28, 42)
sPTD < GA 34^{+0}	130	183 (95-351)	1.40 (0.73-2.69)	214 (3 studies)	⊕⊕⊖⊖ low*	Ref: (19, 28, 43)
Important outcomes						
Perinatal mortality	20	93 (12-731)	4.72 (0.60-37)	121 (1 study)	⊕⊖⊖⊖ very low**	Ref: (28)
PPROM	250	43 (10-185)	0.17 (0.04-0.74)	94 (1 study)	⊕⊖⊖⊖ very low**	Ref: (19)

*Background for evaluation of evidence: 1) The risk of bias was low according to (1), 2) The inconsistency was moderate to high according to I^2 , 3) The indirectness was moderate as risk of sPTD was very high in the included populations, 4) The imprecision was high as the confidence interval included figures which might lead to other conclusions, 5) Due to the small number of participants, we consider the risk of publication bias to be moderate due

sPTD < 37^{+0} weeks even though the Funnel-plot is pretty symmetrical. For sPTD < 34^{+0} weeks we consider the risk of publication bias to be high as the number of participants is low and the Funnel-plot asymmetrical.

Considerations concerning question 10	
Does metronidazole treatment of high risk pregnant women with BV and at any GA reduce the risk of PTD?	
Quality of the evi-dence	Only two of five critical outcomes were addressed of which the Quality of evidence (GRADE) was low. Two important outcomes were addressed of which the quality of evidence (GRADE) was were low
Balance between pro et con	We found no evidence that the intervention is effective concerning the two critical outcomes addressed. Concerning one important outcome (perinatal mortality) the intervention might be harmful.
Values and preferences	We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Clindamycin is probably better than metronidazole (see Question 9 at page 23 and question 11 at page 28)

Rationale for the recommendation (question 10)

We have no evidence that the intervention is effective. The increased perinatal mortality is of concern.

Question 11: High risk, treatment, any GA, clindamycin

Does clindamycin treatment of high risk pregnant women with BV and at any GA reduce the risk of sPTD?
Writer: JS

Recommendation

↓↓: We recommend against treatment of high risk pregnant women for BV at any GA with clindamycin to reduce the risk of sPTD.

Background

BV has been associated with sPTD and clindamycin has been use for treatment of BV in non-pregnant women. Due to an increased focus at these associations a number of pregnant women a high risk of sPTD might be diagnosed with BV.

Literature

Only one study was included (page 68).

Summary of Findings-table – question 11						
Does clindamycin treatment of high risk pregnant women with BV and at any GA reduce the risk of PTD?						
Population: pregnant women with BV at any GA **Intervention:** clindamycin **Control group:** no treatment						
Outcome	**Absolut effect* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of evidence (GRADE)**	**Comments**
	Control	**Clindamycin**				
Critical outcomes						
sPTD < GA 34^{+0}	91	91 (6-1277)	1.00 (0.07-14.1)	22 (1 study)	⊕⊖⊖⊖* very low?	Ref: (44)
Important outcomes: None addressed						
*Background for evaluation of evidence: 1) The risk of bias was low according to (1); 2) The inconsistency could not be evaluated as only one small study was included. This is considered to be a serious limitation; 3) Indirectness was not a limitation; 4) The imprecision was high as the 95%CI included figures which might change the conclusion; 5) The risk of publication bias was very high as only one very small study was included.						

Considerations concerning question 11	
Does clindamycin treatment of high risk pregnant women with BV and at any GA reduce the risk of PTD?	
Quality of the evidence	Only one of five critical outcomes were addressed of which the Quality of evidence (GRADE) was very low. No important outcomes were addressed.
Balance between pro et con	We found no evidence that the intervention is effective. We found no evidence that the intervention is harmful

Values and preferences	We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Based on much a better quality of evidence, we suggest that pregnant women at low risk of sPTD with BV at any GA should not be treated with clindamycin in order to reduce the risk of sPTD (question 9, page **Fejl! Bogmærke er ikke defineret.**).

Rationale for the recommendation (question 11)

Due to the very low quality of the evidence addressing this question, we base our recommendation on that from question 9.

Question 12: High risk, treatment, < 16 weeks, probiotics

Does Probiotics treatment of high risk pregnant women with BV and GA < 16^{+0} reduce the risk of PTD?

Writer: RBH

Recommendation

↓↓: We recommend against treatment of high risk pregnant women for BV before a GA of 16^{+0} weeks with probiotics to reduce the risk of sPTD.

Background

The guideline-group did consider the possible association between probiotics in food and reduced risk of sPTD of relevance of this guideline. Se question 1 at page 9.

Literature

We could not identify studies on this question.

Considerations concerning question 12	
Does Probiotics treatment of high risk pregnant women with BV and GA < 16^{+0} reduce the risk of PTD?	
Quality of the evidence	We could not identify studies on this question
Balance between pro et con	We could not identify studies on this question
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	The indirect evidence in favor of this intervention is very weak. It is likely that antibiotics should be used early in pregnancy before infection/inflammation causes irreversible damage leading to sPTD (5). Most probably, clindamycin is more effective than probiotics at all gestational ages (see question 7 and 9).

Rationale for the recommendation (question 12)

Due to the lack of direct evidence addressing this question, we base the recommendation on indirect evidence from question 7 at page 19.

Question 13: high risk, treatment, GA < 16, metronidazole

Does metronidazole treatment of high risk pregnant women with BV and GA < 16^{+0} reduce the risk of sPTD?
Writer: MAK & KS

Recommendation

↓↓: We recommend against treatment of high risk pregnant women for BV before a GA of 16^{+0} weeks with metronidazole to reduce the risk of sPTD.

Background

We considered this population to be very relevant for treatment of BV as many of these women are interested in relevant intervention. Metronidazole is one the two drugs most often used for BV.

Literature

We could not identify studies which address this question directly.

Considerations concerning question 13	
Does treatment with metronidazole in high risk women with GA < 16 reduce risk of sPTD?	
Quality of the evidence	We could not identify any direct evidence.
Balance between pro et con	We could not identify any direct evidence.
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	It is likely that antibiotics should be used early in pregnancy before infection/inflammation causes irreversible damage leading to sPTD (5). Most probably, clindamycin is more effective than probiotics at all gestational ages (see question 7 and 9).

Rationale for the recommendation (question 13)

Due to the lack of direct evidence addressing this question, we base the recommendation on indirect evidence from question 10 at page 27.

Question 14: High risk, treatment, GA < 16, Clindamycin

Does clindamycin treatment of high risk pregnant women with BV and GA < 16+0 reduce the risk of PTD?
Writer: MAK & KS

Recommendation

↓↓: We recommend against treatment of high risk pregnant women for BV before a GA of 16^{+0} weeks with clindamycin to reduce the risk of sPTD.

Background

We considered this population to be very relevant for treatment of BV as many of these women are interested in relevant intervention. Clindamycin is one the two drugs most often used for BV.

Literature

We could not identify studies which address this question directly.

Considerations concerning question 14	
Does treatment with clindamycin in high risk women with GA < 16 reduce risk of preterm birth.	
Quality of the evidence	We could not identify any direct evidence.
Balance between pro et con	We could not identify any direct evidence.
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	It is likely that antibiotics should be used early in pregnancy before infection/inflammation causes irreversible damage leading to sPTD (5). Most probably, clindamycin is more effective than probiotics at all gestational ages (see question 7 and 9).

Rationale for the recommendation (question 14)

Due to lack of direct evidence, our recommendations are based on the results in PICO 9 (page 23) and PICO 11 (page 28)

Question 15: Symptomatic, any GA, probiotics

Does treatment with Probiotics of symptomatic pregnant women (low and high risk) at any GA with BV reduce the risk of sPTD?
Writer: RBH

Recommendation

↓↓: We recommend against treatment of symptomatic pregnant women for BV at any GA with probiotics to reduce the risk of sPTD.

Background

The guideline-group did consider the possible association between probiotics in food and reduced risk of sPTD of relevance of this guideline. Se question 1 at page 9.

Literature

Only one relevant RCT was identified. As it compared yoghurt with clindamycin, we decided to describe it under question 17 at page 36.

Considerations concerning question 15 Does treatment with Probiotics of symptomatic pregnant women (low and high risk) of any GA with BV reduce the risk of PTD?	
Quality of the evidence	We could not identify any direct evidence.
Balance between pro et con	We could not identify any direct evidence.
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Most probably clindamycin is more effective (se question 3, 9, 11, 14, and 17)

Rationale for the recommendation (question 15)

Due to the lack of direct evidence addressing this question, we base the recommendation on indirect evidence from question 7 at page 19.

Question 16: symptomatic, any GA, metronidazole

Does treatment with metronidazole of symptomatic pregnant women (low and high risk) of any GA with BV reduce the risk of sPTD?
Writer: MAK

Recommendation

↓↓: We recommend against treatment of symptomatic pregnant women for BV at any GA with metronidazol to reduce the risk of sPTD.
However, metronidazole might be used as second choice after clindamycin for treatment of symptoms.

Background

Symptomatic BV (vaginal discharge and/or unpleasant odor) is for some women an uncomfortable disorder, while others are largely unaffected. Therefore, we both considered improved obstetric outcome as well as symptom relieve as relevant clinical factors.

Literature

We could not identify RCT on this question concerning the critical and the important outcomes.

Considerations concerning question 16	
Does treatment with metronidazole of symptomatic pregnant women (low and high risk) of any GA with BV reduce the risk of PTD?	
Quality of the evidence	We could not identify any direct evidence.
Balance between pro et con	We could not identify any direct evidence.
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Most probably, clindamycin is more effective than metronidazole at all gestational ages (see question 8 and 9)

Rationale for the recommendation (question 16)

Due to the lack of direct evidence addressing this question, we base the recommendation on indirect evidence from question 10 at page 27.

Question 17: Symptomatic, any GA, Clindamycin

Does treatment with Clindamycin of symptomatic pregnant (low and high risk) women at any GA with BV reduce the risk of sPTD?
Writer: MAK

Recommendation

↓↓: We recommend against treatment of symptomatic pregnant women for BV at any GA clindamycin to reduce the risk of sPTD.
However, clindamycin might be used for treatment of symptoms.

Background

Symptomatic BV (vaginal discharge and/or unpleasant odor) is for some women an uncomfortable disorder, while others are largely unaffected.

Literature

We could not identify any study evaluating Clindamycin against placebo. One study, however, compared the effect of Clindamycin and probiotics (page 70). The women included were Iranian at low risk of sPTD and the treatment was initiated in the third trimester of pregnancy.

Summary of Finding – question 17

Does treatment with Clindamycin of symptomatic pregnant (low and high risk) women of any GA with BV reduce the risk of PTD?

Population: Symptomatic pregnant women with BV at any GA
Intervention: Clindamycin
Control group: No treatment

Outcome	**Absolut effect* (95% CI)**		**Relative effect** (95% CI)	**Number of participants** (studies)	**Quality of evidence** (GRADE)	**Comments**
	Yoghurt (n/1000)	**Clindamycin** (n/1000)				
Critical outcomes						
sPTD < GA 37^{+0}	80	54 (22-126)	0.67 (0.28-1.58)	300 (1 study)	⊕⊖⊖⊖* **Very low**	
Important outcomes were not addressed						

*Background for evaluation of evidence: 1) The risk of bias was high; 2) The inconsistency could not be evaluated, as only one study was included. This is considered to be a serious limitation; 3) The indirectness is a serious limitation as the control-group received an intervention; 4) The risk of imprecision was low ; 5) The risk of publication bias is very high as only one small study was identifies.

Considerations concerning question 17

Does treatment with Clindamycin of symptomatic pregnant (low and high risk) women of any GA with BV reduce the risk of PTD?

Quality of the evi- dence	Only one critical addressed. The quality of evidence was low. No important outcomes were addressed.
Balance between pro et con	The intervention might reduce the risk of sPTD by 33% which we consider to be of clinical relevance. We found no evidence that the intervention should be harmful.
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Most likely, clindamycin is more effective than metronidazole at all gestational ages (see question 9)

Rationale for the recommendation (question 17)

Due to lack of direct evidence, our recommendations are based on the results in PICO 9 (page 23) and PICO 11 (page 28).

Question 18: High risk with BV, any GA, treatment with Probiotics

Does Probiotics treatment of high risk pregnant women with BV at any GA reduce the risk of PTD?
Writer: RBH

Recommendation

↓↓: We suggest against treatment of high risk pregnant women for BV at any GA weeks with probiotics to reduce the risk of sPTD.

Background

The guideline-group did consider the possible association between probiotics in food and reduced risk of sPTD of relevance of this guideline. Se question 1.

Literature

The only extremely small study addressing this question suggests a negative effect of the intervention.

-

Summary of Findings– question 18						
Does Probiotics treatment of high risk pregnant women with BV at any GA reduce the risk of PTD?						
Population: High risk with BV at any GA **Intervention:** Treatment with probiotics. **Control group:** No treatment.						
Outcome	**Absolut effect* (95% CI)**		**Relative effect** (95% CI)	**Number of participants** (studies)	**Quality of evidence** (GRADE)	**Comments**
	Control (n/1000)	**Intervention** (n/1000)				
Critical outcomes						
sPTD < GA 37^{+00}	nd	nd	nd	35 (1 study)	very low ⊕⊖⊖⊖	Ref: (24) Two of 19 in the intervention group had sPTD, compared to 0/16 in the control group
sPTD < GA 34^{+0}	nd	nd	nd	35 (1 study)	very low ⊕⊖⊖⊖	Ref: (24) One of 19 in the intervention group had sPTD, compared to 0/16 in the control group
Important outcomes						
*Background for evaluation of evidence: 1) The risk of bias high; 2) the inconsistency could not be evaluated as only one study was included. This is considered to be a serious limitation; 3) Indirectness was not a limitation; 4) The risk of imprecision was very high as 95%CI could not be calculated; 5) The risk of publication bias is high as only one very small study was included.						

-

Considerations concerning question 12
Does Probiotics treatment of high risk pregnant women with BV at any GA reduce the risk of PTD?

Quality of the evidence	Two of five critical outcomes were addressed, both with very low quality of evidence.
Balance between pro et con	The intervention might be associated with adverse obstetric outcomes.
Values and preferences	sPTD has serious psychological, health and economic consequences (15-18), why we assume that most women will prefer an intervention which reduces their risk of sPTD. We assume that most Danish women have a dislike toward antibiotics. Thus, a majority of women are expected to prefer alternative treatments to antibiotics if the effects are similar.
Other consideration	Most probably, clindamycin is more effective than probiotics at all gestational ages (see question 8 at page 21 and question 9 at page 23)

Rationale for the recommendation (question 18)

Due to the very low evidence of RCT addressing this question, we base the recommendation on evidence from question 7 at page 19.

Diagnostic criteria - background

Writer: TH

It is generally accepted that the BV-diagnostic gold standards are the Amsel criteria for the clinical use and the Nugent scoring for laboratory use (45).

Amsel criteria - background

The Amsel criteria (46) are fulfilled by the presence of 3 or more of the following elements:

1. Thin, white, homogeneous discharge
2. Clue cells on microscopy
3. pH of vaginal fluid >4.5
4. Release of a fishy odor on adding alkali—10% potassium hydroxide (KOH) solution.

A guideline from the UK mentions that the KOH whiff test cannot be performed because of the caustic nature of KOH (47). They recommend a GRAM stained diagnosis instead.

Nugent score - background

The Nugent score is based on Gram strained preparations (48). Swabs can be performed by the woman herself e.g. by collecting the swab in Eswab Copan(TM) or it can be smeared directly onto a slide with a normal cotton wool swab and left to dry in air (49). A score of 7 to 10 is consistent with BV. The intermediate score of 4-6 is sometimes considered pathogenic but this is debatable (1).

A ready accessible scheme for optimizing and improving objective Nugent Score assessment															
Microscopy *100 x objective															
Number:	*Lactobacillus* morphotype					*Gardnerella*- and *Bacteroides* morphotype					*Mobiluncus* morphotype			*Candida*	
Number of bacteria per field*	0	<1	1-4	5-30	>30	0	<1	1-4	5-30	>30	0	<1-4	>4	0	+
Score	4	3	2	1	0	0	1	2	3	4	0	1	2		
Mark with X															
Total score															

Interpretation				
Total Score	0-3	4-6	7-10	+ candida
	Normal vaginalflora. *Lactobacillus* dominant	No dominant flora. Intermediate.	"*Gardnerella* morphotype" dominant equals BV positive	*Candida* shown
Vaginal Microscopy Workscheme. Doc. 12.8.5. Hospital MIDT, Departement of Microbiology Midt-Vest. Version 4. 22.11.2013.				

Diagnostic question 1: pH-glove (TH)

How accurate is vaginal pH-assessment concerning the BV diagnosis?

Recommendation
↓↓ Clinicians should not use the pH-glove for BV-diagnosis.
↑? Clinicians might consider the pH-glove for BV-screening prior to diagnostic testing.
Background
A vaginal pH above 4.5 has a strong correlation to BV (50, 51). The normal pH of the vagina in Caucasian women ranges between 4.0 and 4.5 (52). It is, however, affected by race (50) semen, vaginal bleeding, vaginal suppositories, and antibiotics (53, 54). The pH can be assessed by indicator paper or the so called Saling glove (55-57, 57, 57, 58).
Literature
We identified 3 studies addressing this question (Se the table below). They all used the Nugent score as gold standard and one demonstrated a relatively low AUC and another low specificity.

Diagnostic question 1: How accurate is vaginal pH-assessment concerning the BV diagnosis?			
Population	Index test (pH>4.5)	Reference (score of 7-10 = BV positive)	Agreement
India (50, 58)	pH glove and pH strip	Nugent Score	AUC = 0.72 (glove) AUC = 0.71 (strip)
USA (50)	Careplan® VpH glove (Saling Glove)	Nugent Score	3D principal component analysis show good agreement
Brasil (51)	0.5 discriminative pH paper	Nugent Score	41% specificity

Rationale for the recommendation
Although the sensitivity is fairly high concerning identification of BV positives pregnant women according to Nugent, the pH-glove has a poor specificity. Thus, if the pH>4.5 the BV diagnosis should confirmed by a subsequent use of a diagnostic tool.

Diagnostic question 2: PCR
How accurate is the PCR-method concerning the BV diagnosis?
Writer: TH
Recommendation
↑↑: We recommend that properly evaluated PCR-techniques are categorized as diagnostic tools for BV, i.e. are used as conclusive alternatives to the Nugent score.

However there is no data available to suggest that one of the qPCR methods is superior to others or to microscopy and the choice should depend on local availability.

Background

Different qPCR assays have been developed to diagnose BV. Mainly these assays detect *Atopobium vaginae* and *Gardnerella vaginalis* above certain threshold levels derived from 16s ribosomal RNA gene copies. The PCR assays minimize intra- and interrater variability which characterize the microscopical assessment. Nevertheless, it should be noted that most PCR assays have been developed by the use of the Nugent score and/or the Amsel´s criteria as reference. Thus the diagnostic values of the PCR assays are not better than well performed reference methods Nugent and/or Amsel criteria. However, the advantage with the PCR methods is that they exclude the controversial Nugent intermediate group, thus the physician is left with a more convenient BV positive or BV negative result. Molecular based methods holds the potential to sub-classify BV into different clusters, but these clusters are yet to be found, are yet to be proven pathogenic and are yet to be assessed in randomized clinical trials.

Literature

We considered 4 different qPCR assays from 4 different groups around the world all demonstrating pretty high sensitivities and specificities when using the Nugent score as the gold standard.

Diagnostic question 2 How accurate is the PCR-method concerning the BV diagnosis?			
Population	Index test (assay)	Reference (score of 7-10 = BV positive)	Agreement
USA (59)	qPCR (*A. vaginae, BVAB-2, and Megasphaera-1*)	Nugent Score	96.7% sensitive 92.2% specificity
Danish (60)	qPCR (*A. vaginae, Prevotella*)	Nugent Score	99% sensitive 90% specificity
French (61)	qPCR (*G. vaginalis* >10^9 copies/mL, *A. vaginae* >10^8 copies/mL)	Nugent Score	95% sensitive 99% specificity
Russian (62)	qPCR (*G. vaginalis, A. vaginae, Lactobacillus spp.* and total quantity of bacterial DNA)	Nugent Score	95.4% sensitive 90.2% specificity

Literature search

Writer: AE

We conducted systematic literature searches relevant to the topic and research questions in the following databases:

- Guidelines International Network: G-I-N
- Medline
- Embase
- The Cochrane Database of Systematic Reviews
- Web of Science
- www.clinicaltrials.gov

Furthermore we searched an international and the Scandinavian, American, British and Canadian national societies of obstetrics and gynecology:

- Dansk Selskab for Obstetrik og Gynækologi (www.dsog.dk)
- Norsk Gynekologisk Forening (www.legeforeningen.no/fagmed/norsk-gynekologisk-forening/)
- Svensk Förening för Obstetrik och Gynekologi (www.sfog.se)
- American Congress of Obstetricians and Gynecologists (www.acog.org)
- The Royal College of Obstetricians and Gynaecologists (www.rcog.org.uk)
- The Society of Obstetricians and Gynaecologist of Canada (www.sogc.org)
- International Federation of Gynecology and Obstetrics (www.figo.org)

G-I-N, Medline, Embase and the Cochrane Database of Systematic Reviews were searched from January 1 2004 to October 3 2014. Web of Science were searched specifically for Scandinavian literature from January 1 1999 to October 3 2014.
All searches were performed with the help of research librarian Hanne Caspersen, Aarhus University Library / Health Science, and/or research librarian Berit Elisabeth Alving, Odense University Hospital.
All citations were managed in an electronic database (RefWorks®).
At least two members of the guideline working group individually reviewed the results of the performed searches and determined eligibility. If there was disagreement between the two guideline working group members, the individual citation's eligibility was discussed between the two members or several members of the guideline working group until an agreement was reached.

The literature searches were performed in several steps:

1. <u>Search for guidelines and systematic reviews I:</u>
   An initial search in G-I-N, Medline and Embase was performed by research librarian Hanne Caspersen using broad search criteria (see search protocol appendix) in order to identify guidelines and systematic reviews. A total of 597 (Medline and Embase) + 6 (G-I-N) unique citations

were identified. Based on titles and abstracts two working group members identified a total of six guidelines and 30 reviews, which were read in full text to decide eligibility, applicability to any of the questions and undergo critical appraisal (see below).

2. Search for guidelines, systematic reviews and primary literature II:
   Another search in Medline, Embase and The Cochrane Database of Systematic Reviews
   with narrower search criteria (see search protocol in appendix) was performed by Berit Elisabeth Alving. A total of 379 unique citations were identified and the guideline working group members identified one guideline, four reviews, five randomized trials and 10 observational studies, which were read in full text to decide eligibility, applicability to any of the questions and undergo critical appraisal.

3. Additional search for literature on probiotics:
   The searches above identified one 2010 systematic review regarding probiotics. The review received a high AMSTAR rating and was considered eligible. A specific search to identify newer studies was performed from 2010 to 2014 using specific search terms (see search protocol in appendix).
   A total of 151 unique citations were identified. Based on titles and abstracts the guideline working group members identified two randomized trials and one observational study, which were read in full text to decide eligibility, applicability and undergo critical appraisal.

4. Additional search for Scandinavian literature:
   In order to identify Scandinavian literature and obtain data on comparable populations and settings an additional search was performed in Web of Science searching on literature originating from Denmark, Norway, Sweden and Finland only, from 1999 to 2014 (see search protocol in appendix).
   A total of 15 unique citations were identified and screened for eligibility. No randomized trials that had not already been identified in the searches above were found. One observational study were found.

5. Search in societies of obstetrics and gynecology :
   National and international societies' webpages were searched for existing guidelines, and two guidelines that had not been identified in the searches described above were identified.

Critical appraisal

AGREE-II
A total of nine guidelines were identified in the searches described above and underwent AGREE-II evaluation by at least two individual working group members to decide the evidence quality and eligibility for this guideline (http://www.agreetrust.org/).
The result of the AGREE-II evaluation is available in appendix X. Four of the guidelines were considered of high quality and are used either directly or as background literature in this guideline.

AMSTAR

A total of 34 (systematic) reviews were read and screened for applicability to any of the research questions. Those that were considered relevant underwent AMSTAR evaluation to by at least two individual working group members to decide the evidence quality and eligibility for this guideline (http://amstar.ca/).

The result of the AMSTAR evaluation is available in appendix X. Three of the systematic reviews were considered eligible, appalicable and of high quality, and are included in this guideline.

For each systematic review / meta-analysis the included randomized studies were scrutinized to decide to which research question they were applicable.

Risk of bias

A total of seven randomized trials, which were not included and therefore not identified through the included high quality systematic reviews, were identified.

Risk of bias was assessed by using the Cochrane risk of bias assessment tool (http://ohg.cochrane.org/sites/ohg.cochrane.org/files/uploads/Risk%20of%20bias%20assessment%20tool.pdf).

Out of the seven trials a total of five trials were included in this guideline.

Review of the included publications

Question 2

Question 2						
Sungkar et al. 2012 (20) Writer: NU	RCT	Influence of early self-diagnosis and treatment of bacterial vaginosis on preterm birth rate				
Population Low risk with BV	Exclusion criteria: Allergy, high risk of PTD, AB < 2 weeks before enrolment Risk status: Low Characteristics: Jakarta, Indonesia					
Intervention	Screening : Yes, 13% were test positive Diagnosis criteria: Nugent score Intervention: n = 176 self-test of pH and metronidazole (500 mg x 2 for 7 days) if positive GA at inclusion: 14-18 weeks					
Control	No screening					
Outcome, critical	Intervention	Control	RR	95%CI	p-value	Comment
sPTD < GA 37	6/176 (3.8%)	8/155 (5.4%)	0.66	0.23 – 1.86	0.43	
Conclusion	The intervention did not reduce the sPTD-rate in a low income setting					
Risk of bias	Random sequence generation (selection bias): low risk Allocation concealment (selection bias): low risk Incomplete outcome data (attrition bias): low risk Selective reporting (reporting bias): low risk Other bias: Very small study Blinding of participants and personnel (performance bias): high risk Blinding of outcome assessment (detection bias): high risk					

Question 3

Question 3		
Kiss 2004 (22) Writer: LW	Study design: RCT-sub-analysis	Title: Prospective randomized controlled trial of an infection screening program to reduce the rate of preterm delivery
Population Asymptomatic, low risk	**Exclusion criteria** used by the RCT: contractions, vaginal bleeding, symptoms of vaginal infection. **Design**: all 4429 participants we screened for BV, Candida vaginalis and Trichomonas. The results of the screening were only released to those randomized for intervention. **Exclusion criteria for this sub-analysis**: participants Candida vaginalis of Trichomonas Intervention group n= 296: T.vag.: 0, candida: 270, BV+T.vag.: 2, BV+candida: 24, all: 0/ Control n=295: T.vag.: 3, candida: 259, BV+T.vag.: 0, BV+candida: 32, all: 1). **Risk status**: low risk, asymptomatic women	

	Characteristics: Austria					
Intervention	**Screening**: yes, GA 15+0-19+6 **Diagnosis**: Nugent score 7-10 and candida species/T. vaginalis on Gram stain **Treatment** BV: Clindamycin treatment (6 days course with 2 % vaginal cream) / re-screening GA 24-27 +/- (7 days course of oral Clindamycin 300 mg x 2). T. vaginalis: Metronidazole (7 days course with 500 mg x 2 orally + partner) / re-screening GA 24-27 Candidiasis: Clotrimazole (6 days course with 0.1 g) / re-screening GA 24-27					
Control	No treatment, standard routine care					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	53/1762 (3.0%)	89/1802 (4.9%)	0.60	0.44;0.85	<0.01	Intervention: (61-8)/(2058-296) (3,0%) Control: (112-23)/(2097-295) (4.9%)
Conclusion	In low risk women, screening for BV and treating with Clindamycin reduces the risk of sPTD < 37 weeks.					
Risk of bias	This a sub-analysis. The effect might be underestimated, as a number of excluded women had other abnormal vaginal flora in combination with BV. sPTD was more frequent among those we excluded from the control in the control group (23/295) than among those we excluded from the intervention group (8/296). This may be explained by an effect of the treatment of candidiasis. The risk of bias was assessed in a Cochrane-review by Brocklehurst et al (2013) (1) who overall found a low risk of bias except on blinding (both personal and participants and at outcome assessment).					

Question 7

Question 7		
Krauss-Silva 2011 (24) Writer: JS	RCT	A randomised controlled trial of probiotics for the prevention of spontaneous preterm delivery associated with bacterial vaginosis: preliminary results
Population Asymptomatic, < 20 weeks, with BV?	Exclusion criteria: ? Risk status: Low risk? I guess they were at low risk (beside their BV-status) Ethnicity/other important characteristics: Brazil	
Intervention	Screening: 4.204 were screened for identification of the BV-postove study-group (N = 644) Diagnosis: vaginal pH >/= 4.5 and Nugent score > 3 (does this mean that they were screened be pH. Only those with pH ≥ 4.5 had an Nugent score?? Treatment: oral administration of selected lactobacilli up to the 24th to 26th week of gestation (N=324).	
Control	Placebo (N=320)	

Outcome, critical	Intervention X/X	Control X/X	OR	95%CI	p	Comment
sPTD < GA 37	5/304	10/301	0.49	0.17, 1.44	0.14	
			0.69	0.26, 1.78	0,30	
sPTD < GA 34	1/304	3/301	0.33	0.03-3.16	0.31	
Infant morbidity		one infant < 34 weeks with respiratory distress syn-drome and suspected early neonatal sepsis.				
Conclusion	Treatment with probiotics in asymptomatic low risk pregnant women in early gestations did not significantly reduce spontaneous preterm delivery before week 34 or week 37.					
Risk of bias	A: Random sequence generation low risk (block randomisation) B: Allocation concealment low risk C: Blinding of participants and personnel blinded D: Blinding of outcome assessment E: Incomplete outcome data High risk (see intention to treat and actual treatment F: Selective reporting G: Other bias brazil, 80% black Sample size The estimated prematurity rate for deliveries at < 34 weeks was 6%; the estimated efficacy was 50%. With a 5% significance level, one- and two-sided tests, and 80% power to detect differences in the premature birth rates between the intervention and placebo groups, the trial sample size was estimated to be 1,140 and 1,480, respectively. Only 642 pregnant women were randomized.						

Question 8

Question 8		
Brocklehurst 2013 (1) Writer: JS	Meta-analyse Cochrane re-view	

Population: BV-positive	Low risk: No previous PTD Screening at any gestational age. Any diagnostic method. Nugent score 4-6 included.					
Intervention	Metronidazole					
Control	placebo or no treatment					
	Intervention	Control	RR	95%CI	p	Comment
Birth < 34	7/242 (2.9%)	6/238 (2.5%)	1.15	0.39-3.36	0.80	
Perinatal death	13/952 (1.4%)	19/965 (2.0%)	0.69	0.34-1.40	0.31	
Risk of bias						

Question 8						
Carey 2000 (26) Writer: RBH	RCT	Title: Metronidazole to prevent preterm delivery in pregnant women with asymptomatical bacterial vaginosis				
Population BV-positive in a obstetric population	Exclusion criteria: increased vaginal discharge with itching, burning, or odor; an allergy to metronidazole; current abuse of ethanol; antibiotic therapy within the previous 14 days; an intention to receive antenatal care or to deliver the infant at a location where the follow-up visit could not be completed or from which information on delivery could not be obtained; planned antibiotic therapy before delivery (excluding intrapartum antibiotic prophylaxis); current or planned cervical cerclage; preterm labor before screening; current or planned tocolytic- drug therapy; fetal death or known life-threatening fetal anomaly; multifetal gestation; or medical illnesses (such as hypertension, preexisting diabetes mellitus, or asthma) that required long-term or intermittent drug therapy. Risk status: low, the entire obstetric population Characteristics: USA with Black 70%, Hispanic 14% non-Hispanic white 14 %					
Intervention	Screening (yes/no, timing): 21.965 women were screened at GA 8^{+0} -22^{+6}, 7393 were BV positive, and 1953 included for randomization Diagnostic criteria: Dacron swab from the vaginal wall. If the pH was >4.4 the Nugent score is performed. BV is present with pH>4.4 and Nugent score =/> 7. Gestational age at randomization: app. at GA 19 Treatment: 8 capsules =2gr metronidazol per oral, repeated after 48 hours. Repeated again 2 gr + 2 gr, before week 30+0, at least 14 days after initial treatment. (32 capsules =8 gr total). The first dose in both series ingested in the presence of study personal.					
Control	Lactose placebo capsules same number and size as treatment capsules					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	116/953=12.2 %	121/966= 12.5%	0.97	0.76-1.23	0.81	
sPTD < GA 34	22/953 = 2.3 %	26/966= 2.7 %	0.86	0.50-1.50	0.59	GA < 32 weeks was used
Outcome, important						

Birth weight <2500 gr <1500 gr	103/953=10.9% 19/953=2%	109/966=11.4% 26/966=2.7%	1.0 0.7	0.7-1.2 0.4-1.3	0.74 0.31	
Side-effects to treatment	21.6%	9.1%				
Risk of bias: low according to (1)						

Question 8						
Okun et al 2005,(63) JS	Systematic review	Antibiotics for Bacterial Vaginosis or *Trichomonas vaginalis* in Pregnancy:				
Population High or low risk of PTD Both symptomatic and asymptomatic women	8 RCT with BV GA at randomization to treatment/control: 13-26 weeks Diagnostic criteria varied between studies.					
Intervention	Oral Metronidazole.					
Control	Placebo or no treatment					
Outcome						
	Intervention	Control X/X	RR	95%CI	P	Comment
Critical o: < 37	228/1681 (13.6%)	210/1676 (12.5%)	1.08	0.73-1.59	0.70	All low and high risk patients
Conclusion	This study does not address the specific PICO because of pooling of high and low risk patients in the analysis of Metronidazole´s effect on reduction of PTD. Though, the systematic review is so well- constructed, and therefore provides us with an aligned answer to our question					
Risk of bias						

Question 8		
McDonald 1997 (25) Writer: JS	Study design RCT	Title: Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis (Gardnerella vaginalis): a RCT
Population BV positive	9407 women were assessed and 2490 were culture positive for a heavy growth of G. vaginalis, or smear positive for BV. 1734 women were eligible and 879 were randomised . 453/872 were both Gram stain positive for BV and culture positive for G.vag.37/872 were Gram stain positive for BV and culture negative. The remainder were culture positive for G.vag and Gram stain negative. Results were unavailable in 7 women Risk status: Low risk Ethnicity/other important characteristics: Australia	
Intervention	Diagnosis: heavy growth of Gardnerella vaginalis or BV by Gram stain	

	Treatment (regime, timing, +/- follow-up): Oral Metronidazole 400 mg x 2 daily for 2 days at 24 weeks of gestation. Test of cure vaginal swabs were taken 4 weeks after treatment (28 weeks). If positive a second course of the allocated treatment was given at 29 weeks.					
Control	Placebo, no treatment, other: Placebo					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < 37^{+0} weeks - subanalysis	11/242 (4.5%)	15/238 (6.3%)	0.72	0.34-1.54		Only smear positive on BV included
Outcome, important						
PPROM	6/242 (2.5%)	10/238 (4.2%)	0.59	0.22-1.60	0.67	BV positive (Smear positive)
Risk of bias	Low risk of bias according to (1) (random sequence generation and allocation concealment unclear risk).					

Question 8						
Odendaal 2002 (28) Writer: AE	**Study design:** RCT	**Title:** Preterm labour – is bacterial vaginosis involved				
Population: Primigravidae, GA 15-26 W, singleton pregnancies, with BV	Exclusion criteria: If history of antibiotics within previous 2 weeks not enrolled immediately but seen and screened after completed antibiotic course. Known cervical incompetence excluded. Risk status: Low Characteristics: South Africa, high prevalence of PTD in study community (20.3%)					
Intervention:	Screening: 1005 were screened to identify the 148 BV-positive included in the study Diagnostic criteria: 3 or more of following 5: grey homogenous discharge, pH > 4.7, positive amine test, 20% or more clue cells, and lactobacilli ≤ 2+. Intervention: Oral metronidazole 400 mg x 2 daily for 2 days. Follow up after 4 weeks. If not resolution same treatment again.					
Control	Vitamin C tablets x 2 daily for 2 days. If BV-positive at follow up after 4 weeks Vitamin C again					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	12/66 (18%)	13/82 (16%)	1.22	0.59-2.49	0.59	
sPTD < GA 34	2/66 (3.0%)	4/82 (4.8%)	0.62	0.06-3.29	0.58	
Outcome, important						
Perinatal mortality	1/66 (1.5%)	2/82 (2.4%)	0.62	0.06-6.70	0.69	
Birth weight: mean (SD)	2989 (536)	2942 (616)	nd	nd	0.62	
Conclusion						
Risk of bias	Random sequence generation (selection bias): Low Allocation concealment (selection bias): Low Incomplete outcome data (attrition bias): Low					

	Selective reporting (reporting bias): Low risk Other bias: Unknown Blinding of participants and personnel (performance bias): Unknown Blinding of outcome assessment (detection bias): Unknown

Question 8						
Moniri 2008 (27) Writer: LH	**Study design:** RCT	**Title:** Effects of Metronidazole Therapy on Preterm Labor in Women with Bacterial Vaginosis				
Population: BV positive population: all women attending the public clinic were recruited. Risk status not given	Exclusion criteria: not mentioned Inclusion: BV in pregnant women GA at inclusion: 20-34 weeks Risk status: probably relative low risk, but it cannot be evaluated due to lack of information concerning parity, twins, other risk factors. Characteristics: Iran					
Intervention	Screening: 420 entered the study , 120 (28,6%) had BV and was randomized into Metronidazol or not. Diagnostic criteria: Amsel Intervention: Metronidazole 500 mg x 2 for 7 days					
Control	No intervention					
Outcome, critical	Intervention	Control X/X	RR	95%CI	p	Comment
sPTD < GA 37	2/60 (3.3%)	2/60 (3.3%)	1.00	0.15-6.87	1.00	Intention-to-treat analysis
Risk of bias	Random sequence generation (selection bias): Not described Allocation concealment (selection bias): Not described Incomplete outcome data (attrition bias): Low Selective reporting (reporting bias): The material and method section is not described in detail at all Other bias: Blinding of participants and personnel (performance bias): low risk (but the participants were told the result of the BV test) Blinding of outcome assessment (detection bias): low risk					

Question 9

Question 9		
Brocklehurst 2013(1) Writer: JS	Meta-analysis Cochrane review (10 studies included)	Antibiotics for treating bacterial vaginosis in pregnancy.

Population	No previous PTD Treatment at any gestational age. Any diagnostic method. Nugent score 4-6 included.					
Intervention	Clindamycin (3 studies metronidazole = 2875) gerne ny Forest plot ed Lene Hee					
Control	placebo or no treatment					
Outcome						
	Intervention	Control	RR	95%CI	p	Comment
Birth < 37	314/3045 (10.3%)	333/3055 (10.9%)	0,95	0,82-1,09	0,46	
Perinatal death	0/395	0/390				
Conclusion						
Risk of bias	Low risk of bias					

Question 9						
Gupta (32) Writer: LW	Study design: RCT	Title: Pregnancy outcome in asymptomatic women with abnormal vaginal flora without any treatment and after treatment with vaginal clindamycin and clotrimazole: A randomized controlled trial				
Population Low risk, asymptomatic women with BV	Exclusion criteria: symptoms of vaginal infections, risk of PTD (vaginal bleeding, twin, essential hypertension, autoimmune disorders, uterine abnormalities, anti-phospholipid syndrome, DM, previous cone biopsy. Exclusion during study: diagnosis of medical disorders Risk status: low risk, asymptomatic women Characteristics: Indian population (New Delhi)					
Intervention	Screening: 800 women were screened to identify the 242 participantsokun . GA at intervention: 12-24 weeks Diagnosis (tool, criteria):Nugent score 7-10 or budding yeast cells/pseudohyphae Treatment: 7-days course of one daily vaginal pessary (clindamycin + clotrimazole, 100 mg each), follow-up after two weeks (not described)					
Control	No treatment					
Outcome, critical	Clindamycin	Control	RR	95%CI	p	Comment
sPTD < GA 37	22/120 (18.6%)	37/122 (30.3%)	0.60	0.38;1.0	0.03	Defined as GA 28-36
sPTD < GA 34	2/120 (1.8%)	9/122 (8.2%)	0.23	0.05;1.0	0.05	Defined as GA 30-33
Late miscarriage	9/120 (7.5%)	13/122 (10.7%)	0.70	0.31;1.6	0.40	Defined as GA 20-27
Outcome, important						
PPROM	10/120 (8.3%)	12/122 (9.5%)	0.85	0.38;1.9	0.41	
Postpartum fever	4/120 (3.3%)	5/122 (4.09%)	0.81	0.22;3.1	0.80	

Conclusion	Screening for BV and candidiasis and vaginal clindamycin+clotrimazole early in pregnancy (GA 12-24) significantly reduce the risk of preterm delivery between GA 28-36 (RR 1.17 95%CI: 1.01;1.35) and between GA 30-34 (RR 1.06 95%CI: 1.00;1.12) in asymptomatic pregnant Indian women. However, the clinical effect might be minimal.
Risk of bias	• Random sequence generation (selection bias): Low risk • Allocation concealment (selection bias): not described • Incomplete outcome data (attrition bias): Low risk. 46 lost to follow-up and 11 developed medical complications (no dropout after randomization) • Selective reporting (reporting bias): • Other bias: • Blinding of participants and personnel (performance bias): Placebo not used, however personel providing routine antenatal care + deliveries blinded • Blinding of outcome assessment (detection bias): Low risk: Placebo not used, however personel providing routine antenatal care + deliveries blinded

Question 9						
Larsson 2006 (64) Writer: MA	RCT Zelen´s design	Title Late miscarriage and preterm birth after treatment with clindamycin: a randomized consent design study according to Zelen				
Population Low risk, BV positive, nullipara (45%) and para (55%)	**Exclusion criteria**: cervical cerclage (n=3), prior clindamycin treatment to sympt. BV (n=1), 13 lost to follow up, smears were lost/not satisfactory for analysis (n=2), therapeutic termination of pregnancy (n=40), early spontaneous miscarriage (n=145), missed miscarriage (n=30) Risk status: low Characteristics: Southeast Health Care region of Sweden					
Intervention	Of 9025 candidates, 234 were excluded 6904 had normal vaginal flora 1068 had intermediate vaginal flora 819 had BV (of these 785 were randomized; the BV diagnosis was only given to those randomized for intervention) Gestational age at inclusion: 10-14 weeks Diagnostic criteria: Nugent score and Hay/Ison criteria to verify (these three tests are equivalent) Intervention: Seven days vaginal clindamycin was started within a week after diagnosis. Follow up in GA 24 and 31 (+/- 2 weeks). Tested again and treated for seven days if positive					
Control	No treatment (Zelen´ s design)					
Outcome, critical	Clindamycin	Control	RR	95%CI	p	Comment

sPTD < GA 37	11/395 (3%)	12/390 (3%)	0.91	0.40-2.0	0.8084	Both sPTD and late miscarriages
sPTD < GA 34	1/395 (0.2%)	5/390 (1%)	0.20	0.02-1.70	0.1409	GA < 33
Outcome, important						
Side effects: Withdraw from treatment because of consistent itching)	3/395 (0.8%)					Data were not available from the study group because of Zelen' s design
NICU-admission	4/395 (1%)	5/390 (1,2%)	0.79	0.21-2.9	0.73	
Conclusion	NICU admission: Intervention group: 18 days of care (range 4-39), cumulative days=223* Control group: 45 days (range 14-94), cumulative days=70* Mann-whitney U test: P=0.14 *Kaplan-Meier, log rank 2.14 (P=0.14)					
Risk of bias	Included in Brocklehurst					

Question 9						
Ugwumadu 2003 (36) Writer: RBH	RCT	Title: Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial				
Population Low risk, asymptomatic with BV	Exclusion criteria: multiple pregnancy; needed or had cervical cerclage; history of cone biopsy; uterine, cervical, or fetal anomaly; disorders such as diabetes, renal disease, collagen disease, lupus, anti-phospholipid syndrome, or essential hypertension; known allergy to clindamycin; or were younger than 16 years of age. Women, who reported a fishy smelling vaginal discharge, either voluntarily or on direct questioning, received treatment and further genitourinary screening for sexually transmitted pathogens, but were excluded from randomization. Risk status: Low risk Characteristics: England, white 60%, black African 10%, black Caribbean 15-18%, Asian 7-8%. 485 women randomized. 244 received clindamycin 207 (85%) had BV, 37 (15%) had intermediate flora. In the placebo group 241 were randomized, 203 (84%) had BV, 38 (16%) had intermediate flora					
Intervention	Screening: 6120 screened between week 12-16 to identify the 485 participants GA at intervention: week 12-16 Diagnostic criteria: Nugent ≥ 7 (740) and Nugent 4-5 Intervention: clindamycin orally 300 mg twice daily 5 days					
Control	Placebo orally twice daily 5 days					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	11/244 (4.5%)	28/241 (11.6%)	0.39	0.20 – 0.76	0.01	
Prior late miscarriage /2nd trimester)	26% 6% (15/240)	34% 9% (20/234)				
Outcome, important						
Birth weight						

<2500 gr <1500 gr	20/240=8% 10/240=4%	23/227=10% 4/227=2%	0.82 2.36	0-46 – 1.46 0.75 – 7.4	p=0.50 p=0.14	
Side-effects to treatment	17/239=7%	8/239=3%			p=0.10	
NICU-admission	18/238=8%	23/228=10%	0.75	0.42 – 1.35	0.34	
Risk of bias: low according to (1)						

Question 9						
Okun et al, (63) Writer: MAK	Systematic review, 5 RCT	Antibiotics for Bacterial Vaginosis or *Trichomonas vaginalis* in Pregnancy: A Systematic Review				
Population	Both high and low risk of PTD. Both symptomatic and asymptomatic women GA at randomization to treatment/control: 12-27 weeks Diagnostic criteria varied between studies.					
Intervention	3 RCT: vaginal cream in 7 days 1 RCT: vaginal cream in 3 days 1 RCT: oral in 5 days					
Control	placebo or no treatment					
	Intervention	Control	RR	95%CI	P	Comment
Critical o: < 37	88/1039 (8.5%)	105/1040 (10.1%)	0.82	0.45-1.50		All low and high risk
This study does not address the specific PICO because of pooling of high and low risk patients in the analysis of Clindamycin´s effect on reduction of PTD. Though, the systematic review is so well-constructed, and therefore provides us with an aligned answer to our question.						

Question 9							
Lamont 2011 (65) Writer; KS & JS	Systematic review/ metaanalysis (5 studies)		Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: A systematic review and metaanalysis				
Population	Low risk, with BV or intermediate flora, treatment GA <22						
Intervention	Clindamycin; vaginal in 4 studies and oral in 1 study.						
Control	No intervention (2 RCT?) or placebo (3 RCT?)						
	No. trials	Intervention	Control	RR	95% CI	p-value	
sPTD < 37	5	44/1183 (3.7%)	72/1163 (6.2%)	0,60	0.42 - 0,85	<.001	
	1 (oral)	11 /244 (4.5%)	28/241 (11.6%)	0.39	0.20 - 0.76	0.01	

	4 (vaginal)	33/939 (3.5 %)	44/922 (4.8%)	0.73	0.47 – 1.15	0.18	
sPTD<33	2	4/639 (0.6%)	9/631 (1.4%)	0.44	0.14 - 1.41	0.17	
Late miscarriage (GA 16-23)	2	2/639 (0.3%)	12/631 (1.9%)	0.16	0.04 – 0.73	0.02	
NICU	1	18/238 (7.6%)	23/228 (10.1%)	0.75	0.42 - 1.35	0.34	
Stillbirth	2	2/386 (0.5)	4/381 (0.49)	0.49	0.09 - 2.67	0.41	
Peripartum infection	1	21/187 (11.2%)	33/188 (17.6%)	0.64	0.38 - 1.06	0.09	
Adverse effects	2	23/426 (5.4%)	14/427 (3.3%)	1.65	0.86 - 3.16	0.13	
Low birth weight	2	38/444 (8.6%)	38/420 (9.0%)	0.95	0.62 - 1.45	0.80	
Risk of bias	AMSTAR score: 11/11						

Question 9						
Lamont 2003 (34) Writer: JS	RCT	Intravaginal clindamycin to reduce preterm birth in with abnormal genital tract floar				
Population Asymptomatic with BV (including intermediate)	Risk status: low GA: 13-20 weeks of gestation Characteristics: UK					
Intervention	Screening: No Diagnosis (tool, criteria): Nugent intermediate flora or BV Treatment: Clindamycin vaginally 100 mg x 1 for 3 nights					
Control	Placebo					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	8/208 (4%)	19/201 (10%)	0.41	0.18 – 0.91	0,03	
Outcome, important						
Perinatal mortality	1/ 208 (1%)	3/201 (2%)	0.32	0.03-3.07	0.32	stillborn
Conclusion						
Risk of bias	Low risk of bias according to (1) (random sequence generation and allocation concealment unclear risk).					

Question 9		
Kiss 2010 (66) Writer: LW	RCT Sub-analysis	Title: Prospective randomized controlled trial of an infection screening program to reduce the rate of preterm delivery
Population Asymptomatic women with BV	The RCT used these exclusion criteria: contractions, vaginal bleeding, symptoms of vaginal infection For this sub-analysis we also excluded 3 BV-positive cases (2 in the intervention group/1 in the control group) who also had candidiasis.	

	Risk status: low risk, asymptomatic women Characteristics: Austria					
Intervention	Screening: 4151 were screened to identify these 192 participants (4.6%) Diagnosis criteria: Nugent score 7-10 GA at randomization: 15+0-19+6 Treatment: Clindamycin treatment (6 days course with 2 % vaginal cream) / re-screening GA 24-27 +/- (7 days course of oral Clindamycin 300 mg x 2).					
Control	No treatment					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	5/149 (3.4%)	8/143 (5.6%)	0.75	0.37-1.50	0.41	
Risk of bias	Performed in a Cochrane-review by Brocklehurst et al (2013) who overall found low risk of bias except on blinding (both personal and participants and at outcome assessment). The study therefore is potential to performance and detection bias. This is a subanalysis conducted by the guideline-group					

Question 9						
Guaschino 2003 (37) Writer: AE	**Study design:** RCT	**Title:** Treatment of asymptomatic bacterial vaginosis to prevent pre-term delivery: a randomized trial.				
Population: Primi- and multigravidae, singleton, asymptomatic BV	Exclusion criteria: Excluded if symptoms of BV or UTI. Risk status: Both low and high risk (8/112 had previous PTD Characteristics: Italy					
Intervention	Screening: 1890 women were screened to identify 112 women with asymptomatic BV. GA at inclusion: 14-25 weeks Diagnosis: Hillier's method (equivalent to Nugent score) Treatment: Clindamycin vaginal cream 2 % x 1 daily for 7 days. Optional control smear at control visit at GA 28-32 weeks.					
Control	No treatment					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	6/49 (12%)	8/51 (16%)	0.78	0.29-2.09	0.62	
Outcome, important						
PPROM	7/49 (14%)	3/51 (5,9%)	2.43	0.67-8.86	0.18	
NICU-admission	9/49 (18%)	15/51 (29%)	0.53	0.25-1.10	0.19	

Risk of bias (Brocklehurst 2013 (1)):

Random sequence generation (selection bias): Low
Allocation concealment (selection bias): Low
Incomplete outcome data (attrition bias): Low
Selective reporting (reporting bias): Low risk
Other bias: Low risk
Blinding of participants and personnel (performance bias): High risk
Blinding of outcome assessment (detection bias): High risk

(8/112 had previous PTD), NB indirectness!
12/112 women were lost to follow up after GW 28-30, NB attribution bias!

Question 9						
Kekki 2001 (33) Writer: TH	RCT	**Title:** Vaginal Clindamycin in Preventing Preterm Birth and Peripartal Infections in Asymptomatic Women With Bacterial Vaginosis: A Randomized, Controlled Trial				
Population: Asymptomatic women with BV	exclusion criteria: Multiple pregnancy, History of preterm birth, Refused, Moved out of town, Induced abortion, Spontaneous abortion					
Intervention:	Screening : 5432 pregnant women screened for BV for inclusion of 375 in this RCT GA at randomization: 12-19 weeks Diagnosis: Spiegels criteria + interobserver validation (93%). The Spiegel criteria are based on the same principles as the Nugent score. Intervention: 2% clindamycin phosphate vaginal cream for 7 days, 2 follow up visits; after 1 week and again mean 34 w GA. However 6% were given additional treatment on mere suspicion of having BV – this is an implication to their randomization!					
Control	An identical-appearing placebo vaginal cream once daily for 7 days Both arms had follow up. This is not entirely clear. I think they were given clindamycin because investigators were blinded to treatment (placebo or clindamycin)					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	9/187 (5%)	7/188 (4%)	1.23	0.49-3.37	0.62	
Outcome, important						
Postpartum fever	11% 21/187	18% 33/188	0.68	0.40-1.13	0.14	
Conclusion	No difference between treatment arm and placebo arm. However among recurrent BV positives they observed a 9-fold increased risk of PTD.					

Risk of bias:

Random sequence generation (selection bias): Low
Allocation concealment (selection bias): Low
Incomplete outcome data (attrition bias): Low
Selective reporting (reporting bias): Low risk
Other bias: low
Blinding of participants and personnel (performance bias): Low
Blinding of outcome assessment (detection bias): Low

However 6% were given additional treatment on mere suspicion of having BV – this is an implication to their randomization!

Question 9						
Larsson 2006 (64) Writer; MAK	RCT	Title Late miscarriage and preterm birth after treatment with clindamycin: a randomized consent design study according to Zelen				
Population Nulliparae (45%) and parae (55%)	**Exclusion criteria**: cervical cerclage (n=3), prior clindamycin treatment to sympt. BV (n=1), 13 lost to follow up, smears were lost/not satisfactory for analysis (n=2), therapeutic termination of pregnancy (n=40), early spontaneous miscarriage (n=145), missed miscarriage (n=30) Risk status: low Characteristics: Southeast Health Care region of Sweden					
Intervention	Of 9025 candidates, 234 were excluded 6904 had normal vaginal flora 1068 han intermediate vaginal flora 819 had BV (of these 785 were randomized; the BV diagnosis was only given to those randomized for intervention) Gestational age at inclusion: 10-14 weeks Diagnostic criteria: Nugent score and Hay/Ison criteria to verify Intervention: Seven days vaginal clindamycin was started within a week after diagnosis. Follow up in GA 24 and 31 (+/- 2 weeks). Tested again and treated for seven days if positive					
Control	No treatment					
Outcome, critical	Intervention X/X	Control X/X	RR	95%CI	p	Comment
sPTD < GA 37	11/395	12/390	0.91	0.40-2.0	0.8084	Both sPTD and late miscarriages
sPTD < GA 34	1/395	5/390	0.20	0.02-1.70	0.1409	GA < 33
Outcome, important						

Perinatal mortality						
Birth weight < 2500	2/11	8/10	0.23	0.06-0.83	0.02	(P=0.009, Fishers exact test)."
Side-effects to treatment	3/X	0/X				Withdraw from treatment because of consistent itching
NICU-admission	4/395	5/390	0.79	0.21-2.9	0.73	
Conclusion	What is Zelen´s design? NICU admission: Intervention group: 18 days of care (range 4-39), cumulative days=223* Control group: 45 days (range 14-94), cumulative days=70* Mann-whitney U test: P=0.14 *Kaplan-Meier, log rank 2.14 (P=0.14)					
Risk of bias	Please add here					

Question 9						
Subtil 2014 (31) Writer: RBH	RCT	Title Early clindamycin for bacterial vaginosis in low-risk pregnancy: The PREMEVA1 randomized multicenter, double-blind, placebo-controlled trial.				
Population Low risk with BV	GA at inclusion: < 15 weeks gestation Risk status: Low risk Characteristics: French maternity wards					
Intervention	Diagnostic criteria): Nugent score>7 Treatment: 1 arm) one four-day course of 600 mg oral clindamycin daily 2 arm) 3 four-day courses of 600 mg oral clindamycin daily, one month apart					
Control	Placebo					
Outcome, critical	Clindamycin	Placebo	RR	95%CI	p	Comment
sPTD < GA 37	91/1904 (4.8%)	39/956 (4.1%)			0.40	
sPTD < GA 34 (12-32 weeks)	22/1904	10/956			0.82	
Outcome, important						
Side-effects to treatment	3.0 %	1.3 %			0.003	
Conclusion	Near identical results in the two groups of low-risk pregnant women with bacterial vaginosis during the first trimester indicate that early treatment with oral clindamycin cannot reduce late abortion or very early preterm spontaneous birth, either preterm birth There is only an abstract available. It looks like they are screening all low-risk pregnant before week 15, and randopmize those with Nugent score>7 to treatment 1 or 2 or placebo. It would be very important to get a full text article, if possible. I will try to contact the author.					

Risk of bias	Random sequence generation (selection bias): Allocation concealment (selection bias): Incomplete outcome data (attrition bias): Selective reporting (reporting bias): Other bias: Blinding of participants and personnel (performance bias): Blinding of outcome assessment (detection bias):

Question 9						
Joesoef 1995 (38) Niels Uldbjerg	RCT	Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight				
Population	Exclusion criteria: allergy, high risk of PTD, AB < 2 weeks before enrolment, Risk status: low Characteristics: Jakarta, Indonesia					
Intervention Low risk with BV	Screening (yes/no, timing): Diagnosis criteria): Nugent Treatment: Clindamycin vaginal cream GA at inclusion: ≤ 20 weeks 147, > 20 weeks 186					
Control	Placebo					
Outcome, critical	Clindamycin	Placebo	RR	95%CI	p	Comment
sPTD < GA 37	51/340 (15.0%)	46/341 (13.5%)	1.11	0.77-1.61	0.57	
sPTD < GA 34	16/340 (4.7%)	9/341 (2.6%)	1.78	0.80-3.98	0.16	< 32 weeks was used
Outcome, important						
Birth weight < 2500g	30/334 (9.0%)	23/338 (6.8%)	1.32	0.78-2.22	0.30	
Side-effects (irritation)	9/340 (2.9%)	6/341 (1.8%)	1.59	0.54-4.18	0.43	
Conclusion						
Risk of bias	Very small study Random sequence generation (selection bias): low risk Allocation concealment (selection bias): low risk Incomplete outcome data (attrition bias): low risk Selective reporting (reporting bias): low risk Other bias: Blinding of participants and personnel (performance bias): low risk					

	Blinding of outcome assessment (detection bias): low risk

Question 10

Question 10						
Brocklehurst 2013(1) Writer: JS	Meta-analyse Cochrane review	Antibiotics for treating bacterial vaginosis in pregnancy.				
Population	High risk: Previous PTD Screening at any gestational age. Any diagnostic method. Nugent score 4-6 included.					
Intervention	Metronidazole (1 study metro plus erythromycin, N 177, Hauth)					
Control	placebo or no treatment					
Outcome						
	Intervention	Control	RR	95%CI	P	Comment
Birth < 37	78/239 (33%)	64/182 (35%)	0,78	0,42-1,48	0,45	
Birth < 34	4/8 (50%)	2/5 (40%)	1,25	0,35-4,49		
Perinatal death	0/25	0/22				
Conclusion						
Risk of bias						

Question 10						
USPSTF 2008 (67) Writer: AE & RBH	Metaanalyse	5 studies (N=3,328) One study (N=168) treated with clilndamycin the rest with metronidazole				
Population	Asymptomatic pregnant women with BV and previous preterm delivery					
Intervention	Three different regimens Metronidazole peroral 400 mg x 2 2 days 250 mg x 3, 7days, 2 gr repeated after 48 hours					
Control	Vitamin c placebo					
	Intervention	Control	RD			Comment
Critical o: < 37	nd	nd	0.1-93	-0.358 - -,029	P	Intervention worse 3 positive 2 negative result

Cri o: <34			0.006	-0.067-0.079		No difference
Conclusion	RR cannot be calculated from the data given? RD means risk reduction.					
Risk of bias						

Question 10						
Honest 2009 (68) Writer: JS	Meta-analyse (5 studies)	Screening to prevent spontaneous preterm birth: Systematic reviews of accuracy and effectiveness literature with economic modelling.				
Population Previous PTD	Screening: no screening GA at randomization: any gestational age. Any diagnostic method. Nugent score 4-6 included.					
Intervention	Metronidazole					
Control	placebo or no treatment					
Outcome						
	Intervention	Control	RR	95%CI	p	Comment
Birth < 37	123/404 (30%)	102/299 (34%)	0.85	0.68 – 1.05	0.30	
Perinatal death	7/87	1/68	5,10	0,65-40,17	0,12	
Conclusion						
Risk of bias	Overall, the quality of the included studies was good with the exception of blinding (allocation concealment).					

Question 10		
USPSTF 2008 (67) Writer: RBH & AE	Metaanalyse	5 studies (N=3,328) One study (N=168) treated with clilndamycin the rest with metronidazole
Population	Asymptomatic pregnant women with BV and previous preterm delivery	
Intervention	Three different oral metronidazole regimens 400 mg x 2 for 2 days 250 mg x 3 for 7days 2 gr repeated after 48 hours	
Control	Vitamin c placebo	

	Intervention	Control	RD			Comment
Critical o: < 37			-0.193	-0.358 - -,029	P	3 positive 2 negative result
Cri o: <34			0.006	-0.067- 0.079		No difference
Conclusion	Intervention worse RD means "Risk reduction"					
Risk of bias						

Question 10						
Okun et al, (63) JS	Systematic review including 8 RCT	Antibiotics for Bacterial Vaginosis or *Trichomonas vaginalis* in Pregnancy:				
Population	All with BV High or low risk of PTD Both symptomatic and asymptomatic women GA at randomization: 13-26 weeks Diagnostic criteria varied between studies.					
Intervention	Oral Metronidazole.					
Control	Placebo or no treatment					
Outcome						
	Intervention	Control X/X	RR	95%CI	P	Comment
Critical o: < 37	228/1681 (13.6%)	210/1676 (12.5%)	1.08	0.73-1.59	0.70	All low and high risk patients
Conclusion	This study does not address the specific PICO because of pooling of high and low risk patients in the analysis of Metronidazole´s effect on reduction of PTD. Though, the systematic review is so well-constructed, and therefore provides us with an alligned answer to our question					
Risk of bias						

Question 10		
Hauth 1995 (42) Writer: KS	RCT, sub-analysis	Title Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis.
Population Prior sPTD BV positive	Primary outcome: 616 women were randomized irrespective of their BV status. This sub-analysis includes only the 177 BV-positive GA at inclusion: 22-24 weeks Exclusion criteria: allergies to metronidazole or erythromycin, uncertain gestational age, multiple pregnancy, prior vaginal bleeding, medical complications, any AV use in the previous 4 weeks, co-infection with gonorrhea, trichomonas or vaginal candida	

	Risk status: high Diagnostic criteria: Amsel's					
Intervention	Interventions: metronidazole 250 mg x 3/day for 7 days plus erythromycin base 333 mg x 3/day for 14 days. Treatment repeated if BV still present at "test-of-cure". Gestational age at trial entry: 22-24 weeks' gestation.					
Control	Placebo					
Outcome, critical	Metronidazole/ erythromycin	Placebo	**Out-come, critical**	Metronidazole/ erythromycin	Pla-cebo	**Outcome, critical**
sPTD < GA 37	47/121(39%)	32/56 (57%)	sPTD < GA 37	47/121(39%)	32/56 (57%)	sPTD < GA 37 The uneven distribution between groups is caused by an 2:1 random-ization.
Risk of bias	Low risk of bias according to (1). Sub-analysis on BV positive Random sequence generation (selection bias): low risk Allocation concealment (selection bias): low risk Incomplete outcome data (attrition bias): low risk Selective reporting (reporting bias): low risk Other bias: Blinding of participants and personnel (performance bias): low risk Blinding of outcome assessment (detection bias): low risk					

Question 10		
Odendaal 2002 (28) Writer: AE	RCT	**Title:** Preterm labour – is bacterial vaginosis involved
Population: BV-pos women with previous PTD or second trimester miscarriage.	Inclusion: Multigravidae with previous PTD or second trimester miscarriage, singleton. GA at inclusion: 15-26 weeks Exclusion criteria: If history of antibiotics within previous 2 weeks not enrolled immediately but seen and screened after completed antibiotic course. Known cervical incompetence excluded. Risk status: High Characteristics: South Africa, high prevalence of PTD in study community (20.3%)	
Intervention:	Screening: 1005 were screened to identify 121 participants.	

	Diagnostic criteria: 3 or more of following 5: grey homogenous discharge, pH > 4.7, positive amine test, 20% or more clue cells, and lactobacilli ≤ 2+. Intervention: Oral metronidazole 400 mg x 2 daily for 2 days. Follow up after 4 weeks. If not resolution same treatment again.					
Control	Placebo, no treatment, other: Oral Vitamin C tablets x 2 daily for 2 days. Follow up after 4 weeks. If not resolution same treatment again.					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	30/70 (43%)	12/51 (24%)	1.82	1.04-3.20	0.04	
sPTD < GA 34	17/70 (24%)	6/51 (12%)	2.06	0.88-4.87	0.10	(note if lower GA-category used)
Outcome, important						
Perinatal mortality	7/70 (1.4%)	1/51 (1.9%)	5.10	0.65-40.2	0.12	
Birth weight: mean (SD)	2475 (980)	2759 (683)			0.07	
Risk of bias:	Random sequence generation (selection bias): Low Allocation concealment (selection bias): Low Incomplete outcome data (attrition bias): Low Selective reporting (reporting bias): Low risk Other bias: Unknown Blinding of participants and personnel (performance bias): Unknown Blinding of outcome assessment (detection bias): Unknown					

Question 10		
McDonald 1997 (25) Writer: JS	Study design RCT	Title: Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis (Gardnerella vaginalis): a RCT
Population BV positive	9407 women were assessed and 2490 were culture positive for a heavy growth of G. vaginalis, or smear positive for BV. 1734 women were eligible and 879 were randomised . 453/872 were both Gram stain positive for BV and culture positive for G.vag.37/872 were Gram stain positive for BV and culture negative. The remainder were culture positive for G.vag and Gram stain negative. Results were unavailable in 7 women. Risk status: High risk Gestational age: 16-26 weeks Ethnicity/other important characteristics: Australia Diagnosis: heavy growth of Gardnerella vaginalis or BV by Gram stain	
Intervention	Treatment (regime, timing, +/- follow-up): Oral Metronidazole 400 mg x 2 daily for 2 days at 24 weeks of gestation. Test of cure vaginal swabs were taken 4 weeks after treatment (28 weeks). If positive a second course of the allocated treatment was given at 29 weeks.	

Control	Placebo, no treatment, other:Placebo					
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment
sPTD < GA 37	1/17 (4.7%)	6/17 ((5.6%)	0.17	0.02-1.24		Sub-analysis
Conclusion						
Risk of bias	Low risk of bias according to (1) (random sequence generation and allocation concealment unclear risk).					

Question 10		
Morales 1994 (19) Writer: MAK	RCT, double blinded	Title Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: A placebo-controlled, double-blind study
Population Singleton, BV positive with prior PTD	Inclusion: Prior PTD, singleton pregnancy Exclusion criteria: Trichomonas infection, (1) significant maternal medical complication including cardiac, respiratory, renal, liver, endocrine, or rheumatic disease, (2) cocaine use in the index pregnancy, (3) the penultimate pregnancy resulted in a preterm birth with a documented intraamniotic or urinary tract infection or if incompetent cervix was judged likely, (4) antibiotics had been used 2 weeks before enrollment, (5) fetal anomalies not consistent with life or polyhydramnios was documented, (6) second-trimester bleeding, and (7) asymptomatic bacteriuria was documented on the initial screen. GA at inclusion: 13-20 weeks Risk status: High Ethnicity/other important characteristics:	
Intervention	Screening: 1992 candidates were screened to identify the 80 participants Diagnosis: Amsel. Intervention: tbl. metronidazole 250mg x 3 a day	
Control	Vitamin C tablet	

Outcome, critical	Intervention X/X	Control X/X	RR	95%CI	p	Comment
sPTD < GA 37	8/44 (18%)	16/36(44%)	0.41	0.198-0.845	0.02	
sPTD < GA 34	2/44(5%)	4/36 (11%)	0.41	0.08-2.1	0.29	
Outcome, important						
Birth weight	6/44 (14%)	12/36(33%)	0.41	0.17-0.98	0.045	Birth weight < 2500g
PPROM	2/44 (5%)	12/36(33%)	0.14	0.03-0.57	0.006	
Risk of bias	Low risk of bias according to (1)					

Question 11

Question 11		

Brocklehurst 2013 (1) Writer: JS	Meta-analyse Cochrane review (1 study included)	Antibiotics for treating bacterial vaginosis in pregnancy.				
Population	Previous PTD Screening at any gestational age. Any diagnostic method. Nugent score 4-6 included.					
Intervention	Clindamycin					
Control	placebo or no treatment					
	Intervention	Control	RR	95%CI	p	Comment
Birth < 34	1/11 (9%)	1/11 (9%)	1,00	0,007-14,1	1.00	
Risk of bias	Low risk of bias					

Question 11						
Okun 2005 (63) JS	Systematic review including 5 RCT	Antibiotics for Bacterial Vaginosis or *Trichomonas vaginalis* in Pregnancy: A Systematic Review				
Population	Pregnant women with BV Both high and low risk of PTD. Both symptomatic and asymptomatic women GA at randomization: 12-27 weeks Diagnostic criteria varied between studies.					
Intervention	3 RCT: vaginal cream in 7 days 1 RCT: vaginal cream in 3 days 1 RCT: oral in 5 days					
Control	placebo or no treatment					
Outcome						
	Intervention	Control	RR	95%CI	P	Comment
sPTD < 37	88/1039 (8.5%)	105/1040 (10.1%)	0.84	0.64 - 1.10	0.20	All low and high risk
This study does not address the specific PICO because of pooling of high and low risk patients in the analysis of Clindamycin´s effect on reduction of PTD. Though, the systematic review is so well-constructed, and therefore provides us with an alligned answer to our question.						

Question 11		

Vermeulen 1999 (44) writer: LH	RCT Sub-analysis	**Title:** Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomized placebo-controlled double-blind trial					
Population: BV-positive, asymptomatic, singleton with prior sPTD	Inclusion: The primary study included 168 which were randomized irrespectively of their BV status. This sub-analysis includes the 22 BV positive participants (by change 11 in each group) Exclusion: PTD because of IUGR, hypertension or pre-eclampsia, placental disorders, congenital uterine anomalies, maternal diseases or known allergy to Clindamycin, Major fetal congenital anomalies in the present pregnancy Risk status: high-risk GA at inclusion: 24-26 weeks. Characteristics: Netherlands						
Intervention	Diagnostic criteria: Nugent score ≥ 7 Intervention: Clindamycin vaginal cream 2 % x 1 daily for 7 days week 26 and 7 days week 32						
Control	Placebo cream for 7 days week 26 and 7 days week 32						
Outcome, critical	Intervention	Control	RR	95%CI	p	Comment	
sPTD < GA 34	10/83 (12%)	4/85 (4.7%)	2.56	0.84-7.84	0.10	Intention-to-treat analysis	
Outcome, important							
PPROM	28/83 (34%)	24/85 (28%)	1.19	0.76-1.88	0.44	Intention-to-treat analysis	
Conclusion							
Risk of bias according to (1)	Random sequence generation (selection bias): Low Allocation concealment (selection bias): Low Incomplete outcome data (attrition bias): Low Selective reporting (reporting bias): Low risk Other bias: Low risk Blinding of participants and personnel (performance bias): Low risk Blinding of outcome assessment (detection bias): Low risk						

Question 17

Question 17		
Hantoushzadeh 2012 (69) Writer: RBH	RCT	Title: Comparative efficacy of probiotic yoghurt and clindamycin in treatment of bacterial vaginosis in pregnant women: A randomized clinical trial
Population Symptoms of BV	Exclusion criteria: UTI, prior PTD, PPROM, underlying disease, other infections GA at randomization: 3 trimester of pregnancy Risk status: (high/low/definition) low risk () Characteristics: Iran ?	
Intervention	Diagnostic criteria: Amsel at least 3 criteria	

	Intervention: probiotic yoghurt 100 gr twice a day one week					
Control	Clindamycin 300 mg per oral twice a day one week					
Outcome, critical	Yoghurt	Clindamycin	RR	95%CI	p	Comment
sPTD < GA 37	12/150 (8%)	8/150 (5.3%)	1.5	0.63 – 3.56	0.36	
Risk of bias	• Random sequence generation (selection bias): • Allocation concealment (selection bias): computer generated sequence • Incomplete outcome data (attrition bias): As the women were included i 3 trimester in Gestational age (Weeks) 36.43 ± 1.32 (probiotic) 36.31 ± 1.28 (clindmycin) this publication does not concern most of our outcome variables • Selective reporting (reporting bias): • Other bias: • Blinding of participants and personnel (performance bias): double-blind • Blinding of outcome assessment (detection bias): follow up by telephone interview for symptoms of recurrence, treatment blinded					

Diagnostic question 1

Diagnostic question 1				
Hemalatha 2013? (58) Writer: TH	Observational (cross sectional)	Evaluation of vaginal pH for detection of bacterial vaginosis		
Population	270 non-pregnant women with complaints of discharge, back pain and abdominal pain			
Index test	pH glove and pH strip Comment: They make a quality control with a pH-meter and narrow range pH-paper (3,5-5,2)			
Reference	Nugent score ≥ 7-10			
Method	Sensitivity	Specificity	AUC	
Strip	72%	60%	0,71	
Glove	79%	53 %	0,72	
Conclusion				
Risk of bias				

Diagnostic question 1		
Ravel et al 2011? (50) Writer: TH	Observational	The microbiome of reproductive aged women
Population	396 non-pregnant asymptomatic women 12-45 years	

Index test	pH glove (vpH)	
Reference	Nugent score ≥ 7	
Outcome	BV +/-	
Conclusion	Strong correlation between pH and Nugent score depicted by 3D principal component analysis	Microbiome approach: Authors report that a high pH where strongly related to vaginal microcommunities that were not dominated by lactobacillus spp.. However they also state: "Interestingly, elevated pH and high Nugent scores were observed in some microbial communities that have high proportions of Lactobacillus species"
Important:		

Diagnostic question 1			
Krauss-Silva 2014 Writer: TH	Observational/Screening	Basic vaginal pH, bacterial vaginosis and aerobic vaginitis: prevalence in early pregnancy and risk of spontaneous preterm delivery, a prospective in a low socioeconomic and multiethnic South American population.	
Population	1699 pregnant women attending prenatal clinic, screening before 20 w GA		
Index test	with 0,5 discriminative pH-paper		
Gold standard	Nugent ≥ 7		
	Sensitivity	Specificity	Comment: Show that there is an increased risk for BV positive women initially screened by pH.
pH>4,5	100 %	41%	
pH>5,0	82%	84%	
Important:	Only a subset of 100 patients with pH<4.5 were screened for BV and among these none had BV by Nugent score. It seems that the authors extrapolated these finding for the remaining 392 patients with pH<4.5 in table 6 although it is possible that there could have been BV positives among patients with pH<4.5. Thus the sensitivity may only be theoretical.		

Diagnostic question 2

Diagnostic question 2		
Cartwright 2012 Writer: TH	Observational	Development and validation of a semiquantitative, multitarget PCR assay for diagnosis of bacterial vaginosis
Population	402 non-pregnant Women attending STD clinic, no antibiotics, no vaginal medicine, Only a subset of 100 patients with pH<4.5 were screened for BV and among these none had BV by Nugent score. It seems that the authors extrapolated these finding for the remaining 392 patients with pH<4.5 in table 6 although it is possible that there could have been BV positives among patients with pH<4.5. Thus the sensitivity may only be theoretical.	
Index test	PCR assay: Lactobacillus crispatus, A. vaginae, BVAB-2, and Megasphaera-1	

Gold standard	Nugent score ≥ 7 or Nugent score 4-6 that met Amsel criteria		
Index test	BV +/- by PCR		
	Sensitivity	Specificity	
	96.7%	92.2%	

Diagnostic question 2			
Shipitsyne 2013 (60) Writer: TH	Observational	The composition of the vaginal microbioma in women of reproductive age – sensitive and specific molecular diagnosis of bacterial vaginosis is possible	
Population	163 non-pregnant unselected women, mean age 26, no antibiotic treatment		
Index test	PCR assay: (lactobacillus spp. relative <47%, A. vaginae, Prevotella and G.vaginalis)		
Reference test	Amsel		
	Sensitivity	Specificity	
	100%	95%	
Comment	Danish study, SSI		

Diagnostic question 2			
Menard 2010 (61) Writer: R	Observational	Diagnostic accuracy and quantitative real-time PCR assay versus clinical and Gram stain identification of bacterial vaginosis	
Population	163 pregnant women 18+, presenting with vaginal symptoms		
Index test	PCR assay: (lactobacillus spp. relative <47%, A. vaginae, Prevotella and G.vaginalis)		
Reference test	BV-positive samples were those with NS values of 7 to 10 + positive AMSEL		
Outcome	BV +/-		
	Sensitivity	Specificity	This French facility use PCR diagnostics in their obstetrical department
	100%	93%	

Diagnostic question 2		
Rumyantseva 2014 (62) Writer: TH	Observational	Utility of microscopic techniques and quantitative polymerase chain reaction for the diagnosis of vaginal microflora alterations.
Population	100 caucasian women	

Index test	PCR assay: (Gardnerella vaginalis, Atopobium vaginae, Lactomacillus species, and total quantity of bacterial DNA		
Reference test	BV-positive samples were those with NS values of 7 to 10		
	Sensitivity	Specificity	
	95.4 %	90,2%	
Comments	Commercially available		

Forrest plots and Funnel plots

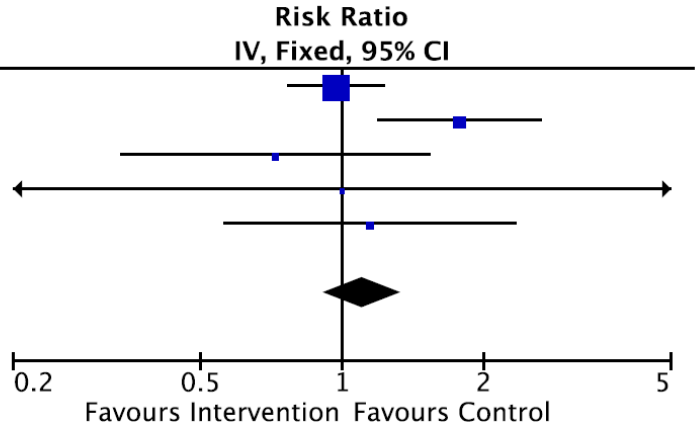
Writer: LE

Question 8; sPTD < 37^{+0} weeks

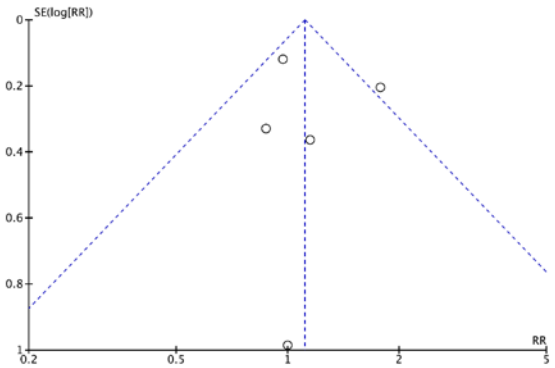
Does metronidazole treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: sPTD < 37^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Carey 2000 (1)	116	953	121	966	63.5%	0.97 [0.77, 1.23]
Klebanoff 2001 (2)	60	315	31	289	22.2%	1.78 [1.19, 2.66]
McDonald 1997 (3)	11	242	15	238	6.3%	0.72 [0.34, 1.54]
Moniri 2008 (4)	2	60	2	60	1.0%	1.00 [0.15, 6.87]
Odendaal 2002 (5)	12	66	13	82	7.1%	1.15 [0.56, 2.34]
Total (95% CI)		**1636**		**1635**	**100.0%**	**1.10 [0.91, 1.33]**
Total events	201		182			

Heterogeneity: $Chi^2 = 7.68$, df = 4 (P = 0.10); $I^2 = 48\%$
Test for overall effect: Z = 1.02 (P = 0.31)



Footnotes
(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved
(5) Cochrane approved



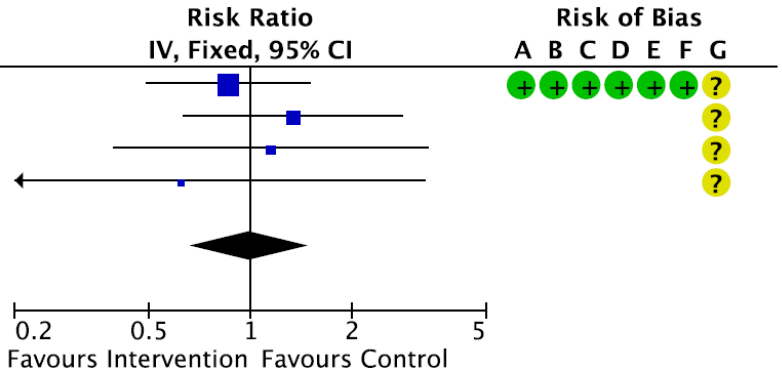
Question 8; sPTD < 34^{+0} weeks

Does metronidazole treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: sPTD < 34^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Carey 2000 (1)	22	953	26	966	51.5%	0.86 [0.49, 1.50]
Klebanoff 2001 (2)	16	315	11	289	28.7%	1.33 [0.63, 2.83]
McDonald 1997 (3)	7	242	6	238	14.0%	1.15 [0.39, 3.36]
Odendaal 2002 (4)	2	66	4	82	5.8%	0.62 [0.12, 3.29]
Total (95% CI)		**1576**		**1575**	**100.0%**	**1.00 [0.67, 1.49]**
Total events	47		47			

Heterogeneity: $Chi^2 = 1.23$, df = 3 (P = 0.75); $I^2 = 0\%$

Test for overall effect: Z = 0.02 (P = 0.98)



Footnotes

(1) Not Cochrane approved

(2) GA < 32 weeks, Cochrane approved

(3) Cochrane approved

(4) Cochrane approved

Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

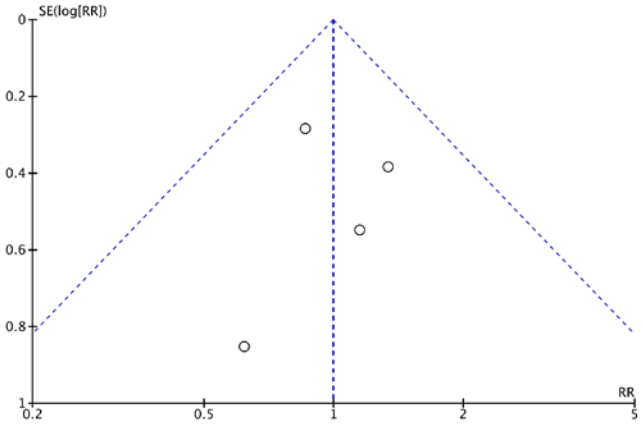
(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

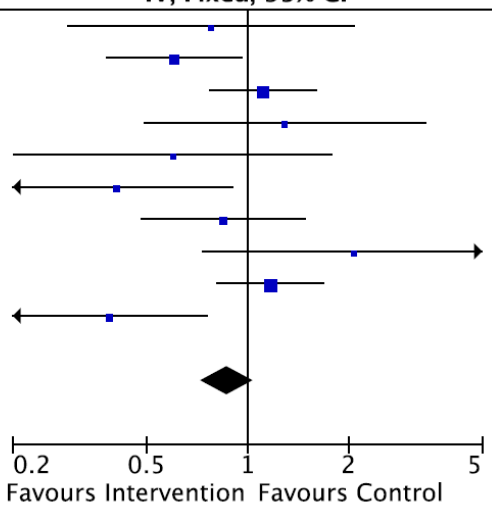


Question 9, sPTD < 37^{+0} weeks

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: sPTD < 37^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Guashino 2003 (1)	6	49	8	51	3.4%	0.78 [0.29, 2.09]	?
Gupta 2014	22	120	37	122	15.4%	0.60 [0.38, 0.96]	
Joesof 1995 (2)	51	340	46	341	24.3%	1.11 [0.77, 1.61]	?
Kekki 2001 (3)	9	187	7	188	3.5%	1.29 [0.49, 3.40]	?
Kiss 2004 (4)	5	149	8	143	2.8%	0.60 [0.20, 1.79]	?
Lamont 2003 (5)	8	208	19	201	5.1%	0.41 [0.18, 0.91]	?
Larsson 2006 (6)	21	408	25	411	10.4%	0.85 [0.48, 1.49]	?
McGregor 1994 (7)	9	60	5	69	3.1%	2.07 [0.73, 5.84]	+ + ?
Subtil 2014 (8)	91	1904	39	956	24.6%	1.17 [0.81, 1.69]	?
Ugwumadu 2003 (9)	11	244	28	241	7.3%	0.39 [0.20, 0.76]	?
Total (95% CI)		**3669**		**2723**	**100.0%**	**0.87 [0.73, 1.05]**	
Total events	233		222				

Heterogeneity: $Chi^2 = 19.37$, df = 9 (P = 0.02); $I^2 = 54\%$
Test for overall effect: Z = 1.47 (P = 0.14)



Footnotes
(1) 8/112 had previous PTD. Cochrane approed
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved
(5) Cochrane approved
(6) Cochrane approved
(7) Not Cochrane approved
(8) Not Cochrane approved
(9) Cochrane approved

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

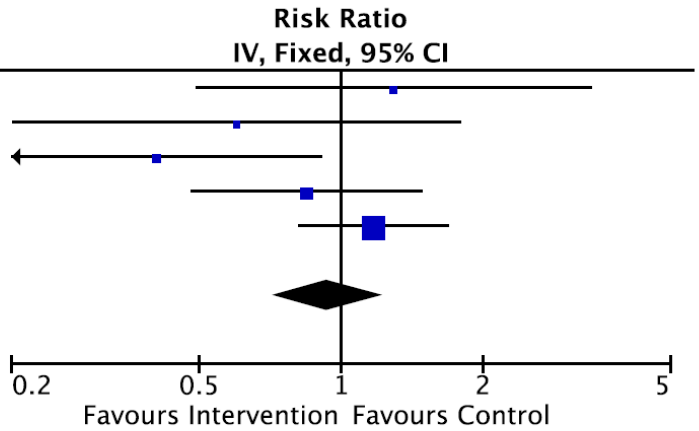
Question 9, a subanalysis, sPTD < 37+0 weeks, (only studies with intervention before 20^{+0} weeks)

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Subanalysis including only studies with intervention before 20^{+0} weeks
Outcome: sPTD < 37^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Kekki 2001 (1)	9	187	7	188	7.6%	1.29 [0.49, 3.40]
Kiss 2004 (2)	5	149	8	143	6.0%	0.60 [0.20, 1.79]
Lamont 2003 (3)	8	208	19	201	11.1%	0.41 [0.18, 0.91]
Larsson 2006 (4)	21	408	25	411	22.4%	0.85 [0.48, 1.49]
Subtil 2014 (5)	91	1904	39	956	52.9%	1.17 [0.81, 1.69]
Total (95% CI)		**2856**		**1899**	**100.0%**	**0.94 [0.72, 1.23]**
Total events	134		98			

Heterogeneity: $Chi^2 = 6.76$, df = 4 (P = 0.15); $I^2 = 41\%$

Test for overall effect: Z = 0.47 (P = 0.64)



Footnotes

(1) Cochrane approved

(2) Cochrane approved

(3) Cochrane approved

(4) Cochrane approved

(5) Not Cochrane approved

Question 9, a subanalysis, sPTD < 37^{+0} weeks

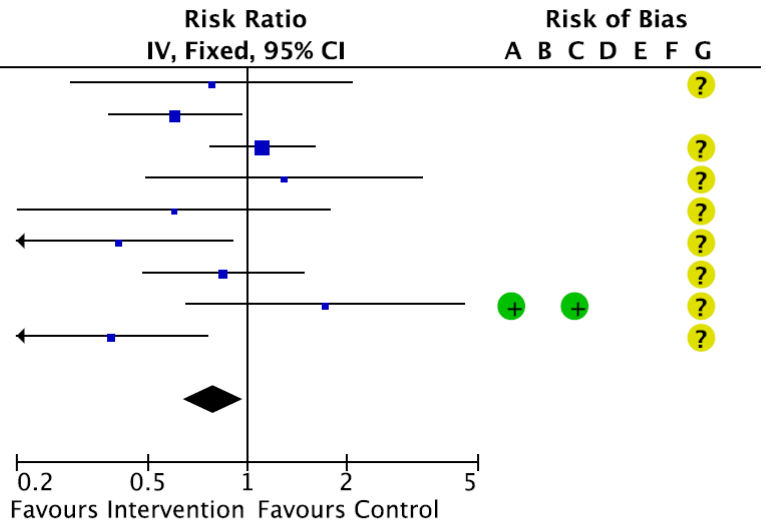
Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?

Subanalysis excluding ref (31)

Outcome: sPTD < 37^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Guashino 2003 (1)	6	49	8	51	4.5%	0.78 [0.29, 2.09]
Gupta 2014	22	120	37	122	20.3%	0.60 [0.38, 0.96]
Joesoef 1995 (2)	51	340	46	341	32.1%	1.11 [0.77, 1.61]
Kekki 2001 (3)	9	187	7	188	4.7%	1.29 [0.49, 3.40]
Kiss 2004 (4)	5	149	8	143	3.7%	0.60 [0.20, 1.79]
Lamont 2003 (5)	8	208	19	201	6.8%	0.41 [0.18, 0.91]
Larsson 2006 (6)	21	408	25	411	13.7%	0.85 [0.48, 1.49]
McGregor 1994 (7)	9	60	6	69	4.6%	1.73 [0.65, 4.57]
Ugwumadu 2003 (8)	11	244	28	241	9.6%	0.39 [0.20, 0.76]
Total (95% CI)		**1765**		**1767**	**100.0%**	**0.79 [0.64, 0.97]**
Total events	142		184			

Heterogeneity: $Chi^2 = 15.24$, df = 8 (P = 0.05); $I^2 = 47\%$
Test for overall effect: Z = 2.21 (P = 0.03)



Footnotes
(1) 8/112 had previous PTD, Cochrane approved
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved
(5) Cochrane approved
(6) Cochrane approved
(7) Not Cochrane approved
(8) Cochrane approved

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

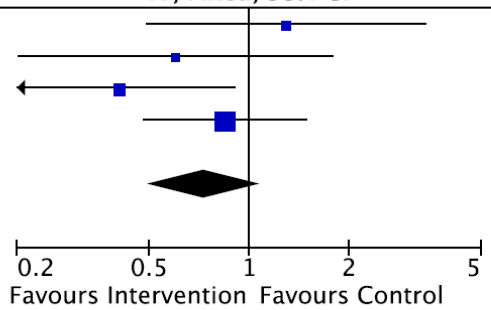
Question 9, a subanalysis, sPTD < 37+0 weeks

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Subanalysis including only studies with intervention before 20^{+0} weeks and excluding ref (31)
Outcome: sPTD < 37^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Kekki 2001 (1)	9	187	7	188	16.2%	1.29 [0.49, 3.40]	?
Kiss 2004 (2)	5	149	8	143	12.7%	0.60 [0.20, 1.79]	?
Lamont 2003 (3)	8	208	19	201	23.5%	0.41 [0.18, 0.91]	?
Larsson 2006 (4)	21	408	25	411	47.6%	0.85 [0.48, 1.49]	?
Total (95% CI)		**952**		**943**	**100.0%**	**0.73 [0.50, 1.08]**	
Total events	43		59				

Heterogeneity: $Chi^2 = 3.76$, df = 3 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 1.58 (P = 0.11)



Footnotes

(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved

Risk of bias legend

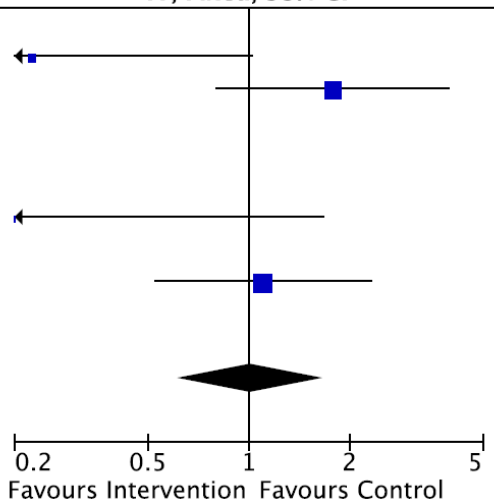
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Question 9, sPTD < 34^{+0} weeks

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: sPTD < 34^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
Guashino 2003 (1)	0	0	0	0		Not estimable							?
Gupta 2014	2	120	9	122	10.9%	0.23 [0.05, 1.02]							
Joesoef 1995 (2)	16	340	9	341	38.6%	1.78 [0.80, 3.98]							?
Kekki 2001 (3)	0	0	0	0		Not estimable							?
Kiss 2004 (4)	0	0	0	0		Not estimable							?
Lamont 2003 (5)	0	0	0	0		Not estimable							?
Larsson 2006 (6)	1	395	5	390	5.4%	0.20 [0.02, 1.68]							?
McGregor 1994 (7)	0	0	0	0		Not estimable	+		+				?
Subtil 2014 (8)	22	1904	10	956	45.0%	1.10 [0.53, 2.32]							?
Ugwumadu 2003 (9)	0	0	0	0		Not estimable							?
Total (95% CI)		**2759**		**1809**	**100.0%**	**1.02 [0.62, 1.68]**							
Total events	41		33										

Heterogeneity: $Chi^2 = 7.98$, df = 3 (P = 0.05); $I^2 = 62\%$
Test for overall effect: Z = 0.07 (P = 0.94)



Footnotes
(1) 8/112 had previous PTD, Cochrane approved
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved
(5) Cochrane approved
(6) Cochrane approved
(7) Not Cochrane approved
(8) Not Cochrane approved
(9) Cochrane approved

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Question 9; a subanalysis, sPTD < 34^{+0} weeks, (only studies with intervention before 20^{+0} weeks)

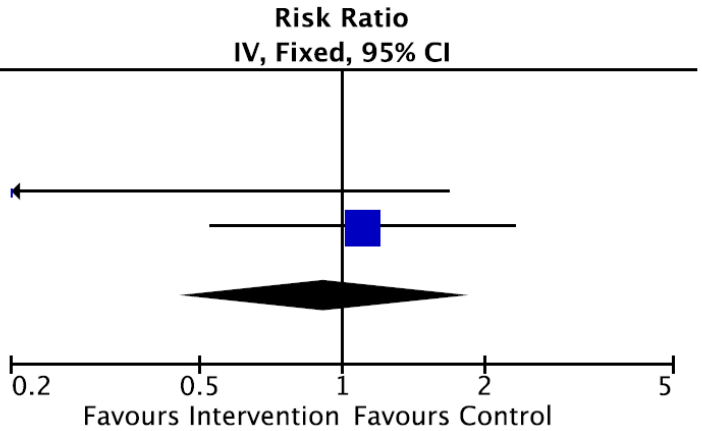
Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Subanalysis including only studies with intervention before 20^{+0} weeks

Outcome: sPTD < 34^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Kekki 2001 (1)	0	0	0	0		Not estimable
Kiss 2004 (2)	0	0	0	0		Not estimable
Lamont 2003 (3)	0	0	0	0		Not estimable
Larsson 2006 (4)	1	395	5	390	10.7%	0.20 [0.02, 1.68]
Subtil 2014 (5)	22	1904	10	956	89.3%	1.10 [0.53, 2.32]
Total (95% CI)		**2299**		**1346**	**100.0%**	**0.92 [0.45, 1.85]**
Total events	23		15			

Heterogeneity: $Chi^2 = 2.21$, df = 1 (P = 0.14); $I^2 = 55\%$

Test for overall effect: Z = 0.24 (P = 0.81)



Footnotes

(1) Cochrane approved

(2) Cochrane approved

(3) Cochrane approved

(4) Cochrane approved

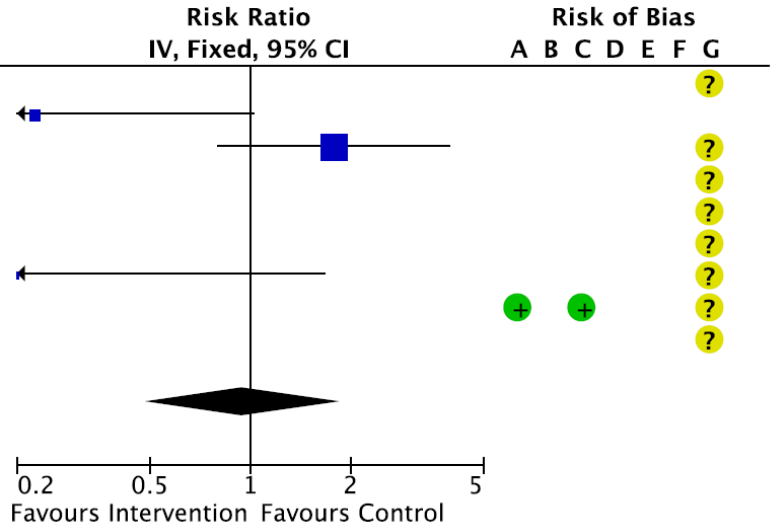
(5) Not Cochrane approved

Question 9, a subanalysis, sPTD < 34^{+0} weeks

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
A subanalysis not including ref (31)
Outcome: sPTD < 34^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Guashino 2003 (1)	0	0	0	0		Not estimable
Gupta 2014	2	120	9	122	19.8%	0.23 [0.05, 1.02]
Joesoef 1995 (2)	16	340	9	341	70.3%	1.78 [0.80, 3.98]
Kekki 2001 (3)	0	0	0	0		Not estimable
Kiss 2004 (4)	0	0	0	0		Not estimable
Lamont 2003 (5)	0	0	0	0		Not estimable
Larsson 2006 (6)	1	395	5	390	9.9%	0.20 [0.02, 1.68]
McGregor 1994 (7)	0	0	0	0		Not estimable
Ugwumadu 2003 (8)	0	0	0	0		Not estimable
Total (95% CI)		**855**		**853**	**100.0%**	**0.95 [0.49, 1.87]**
Total events	19		23			

Heterogeneity: $Chi^2 = 7.90$, df = 2 (P = 0.02); $I^2 = 75\%$
Test for overall effect: Z = 0.14 (P = 0.89)



Footnotes
(1) 8/112 had previous PTD, Cochrane approved
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved
(5) Cochrane approved
(6) Cochrane approved
(7) Not Cochrane approved
(8) Cochrane approved

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

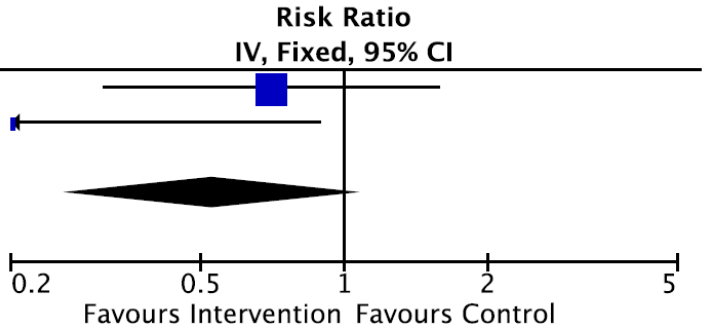
Question 9, late miscarriage

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: Late miscarriage

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Gupta 2014	9	120	13	122	77.5%	0.70 [0.31, 1.58]
Ugwumadu 2003	2	244	10	241	22.5%	0.20 [0.04, 0.89]
Total (95% CI)		**364**		**363**	**100.0%**	**0.53 [0.26, 1.08]**
Total events	11		23			

Heterogeneity: $Chi^2 = 2.12$, df = 1 (P = 0.15); $I^2 = 53\%$

Test for overall effect: Z = 1.75 (P = 0.08)



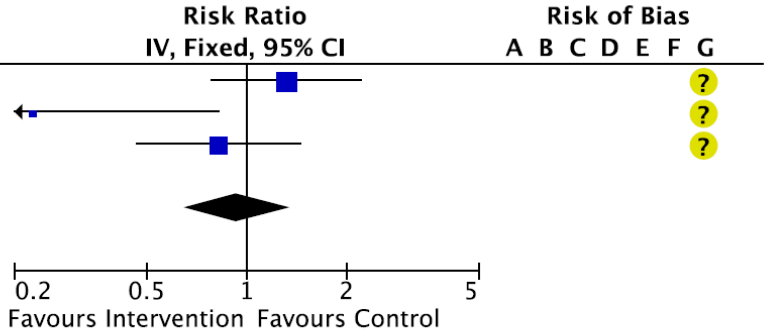
Question 9, Birth weight < 2500g

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?

Outcome: Birth weight < 2500 g

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Joesoef 1995 (1)	30	334	23	338	50.1%	1.32 [0.78, 2.22]
Larsson 2006 (2)	2	11	8	10	8.2%	0.23 [0.06, 0.83]
Ugwumadu 2003 (3)	20	240	23	227	41.8%	0.82 [0.46, 1.46]
Total (95% CI)		**585**		**575**	**100.0%**	**0.94 [0.65, 1.36]**
Total events	52		54			

Heterogeneity: $Chi^2 = 6.48$, df = 2 (P = 0.04); $I^2 = 69\%$
Test for overall effect: Z = 0.34 (P = 0.73)



Footnotes
(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved

Risk of bias legend
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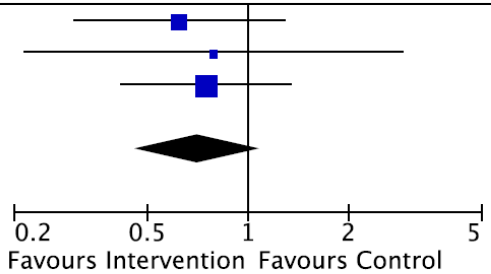
(**G**) Other bias

Question 9, NICU admission

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: NICU admission

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Guashino 2003 (1)	9	49	15	51	35.3%	0.62 [0.30, 1.29]	?
Larsson 2006 (2)	4	395	5	390	10.9%	0.79 [0.21, 2.92]	?
Ugwumadu 2003 (3)	18	238	23	228	53.8%	0.75 [0.42, 1.35]	?
Total (95% CI)		**682**		**669**	**100.0%**	**0.71 [0.46, 1.09]**	
Total events	31		43				

Heterogeneity: $Chi^2 = 0.18$, df = 2 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 1.57 (P = 0.12)



Footnotes
(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved

Risk of bias legend
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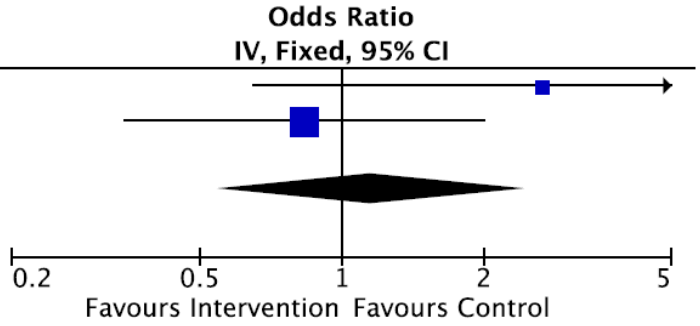
Question 9, PPROM

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: PPROM

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Guashino 2003	7	49	3	51	27.9%	2.67 [0.65, 10.97]
Gupta 2014	10	120	12	122	72.1%	0.83 [0.35, 2.01]
Total (95% CI)		**169**		**173**	**100.0%**	**1.15 [0.55, 2.43]**
Total events	17		15			

Heterogeneity: $Chi^2 = 1.87$, df = 1 (P = 0.17); $I^2 = 47\%$
Test for overall effect: Z = 0.37 (P = 0.71)

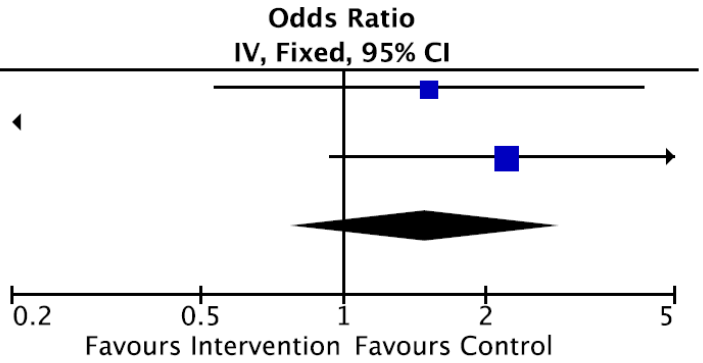


Question 9: Side effects

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: Side effects

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Joesoef 1995 (1)	9	340	6	341	38.9%	1.52 [0.53, 4.31]
Larsson 2006 (2)	3	395	1	1	3.7%	0.00 [0.00, 0.09]
Ugwumadu 2003 (3)	17	239	8	239	57.3%	2.21 [0.94, 5.23]
Total (95% CI)		**974**		**581**	**100.0%**	**1.49 [0.78, 2.86]**
Total events	29		15			

Heterogeneity: $Chi^2 = 13.89$, df = 2 (P = 0.0010); $I^2 = 86\%$
Test for overall effect: Z = 1.20 (P = 0.23)



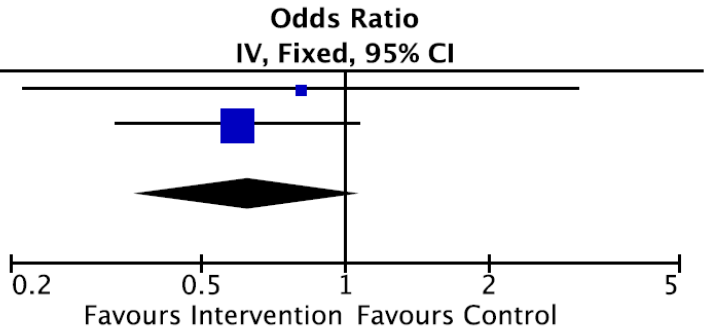
Footnotes
(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved

Question 9: Postpartum fever

Does clindamycin treatment of low risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: Postpartum fever

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Gupta 2014	4	120	5	122	16.2%	0.81 [0.21, 3.08]
Kekki 2001	21	187	33	188	83.8%	0.59 [0.33, 1.07]
Total (95% CI)		**307**		**310**	**100.0%**	**0.62 [0.36, 1.07]**
Total events	25		38			

Heterogeneity: $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 1.71 (P = 0.09)



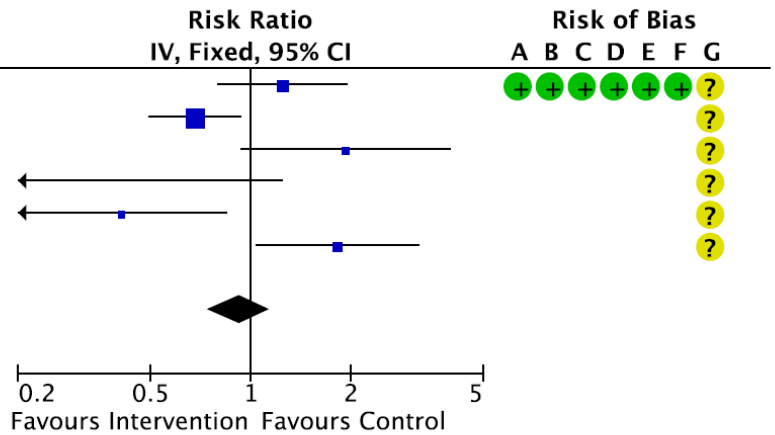
Question 10: sPTD < 37^{+0} weeks

Does metronidazole treatment of high risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: sPTD < 37^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Carey 2000 (1)	30	101	26	109	22.5%	1.25 [0.79, 1.95]
Hauth 2014 (2)	47	121	32	56	44.8%	0.68 [0.49, 0.93]
Klebanoff 2001 (3)	16	32	7	27	8.6%	1.93 [0.93, 3.98]
McDonald 1997 (4)	1	17	6	17	1.1%	0.17 [0.02, 1.24]
Morales 1994 (5)	8	44	16	36	8.6%	0.41 [0.20, 0.85]
Odendaal 2002 (6)	30	70	12	51	14.3%	1.82 [1.04, 3.20]
Total (95% CI)		**385**		**296**	**100.0%**	**0.92 [0.75, 1.14]**
Total events	132		99			

Heterogeneity: $Chi^2 = 22.41$, df = 5 (P = 0.0004); $I^2 = 78\%$

Test for overall effect: Z = 0.72 (P = 0.47)



Footnotes

(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved
(4) Cochrane approved
(5) Cochrane approved
(6) Cochrane approved

Risk of bias legend

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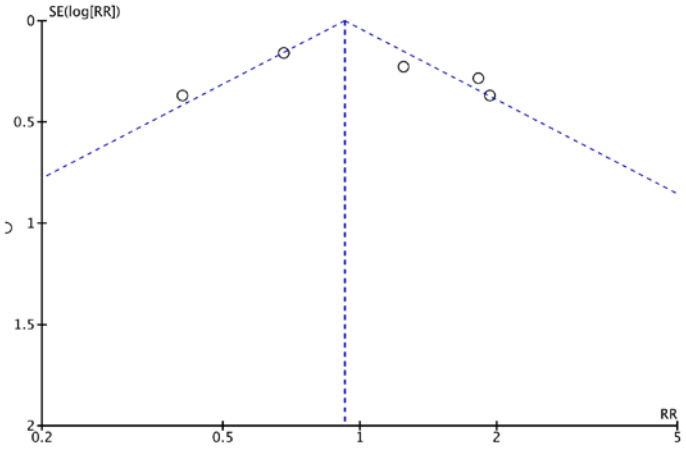
(**G**) Other bias

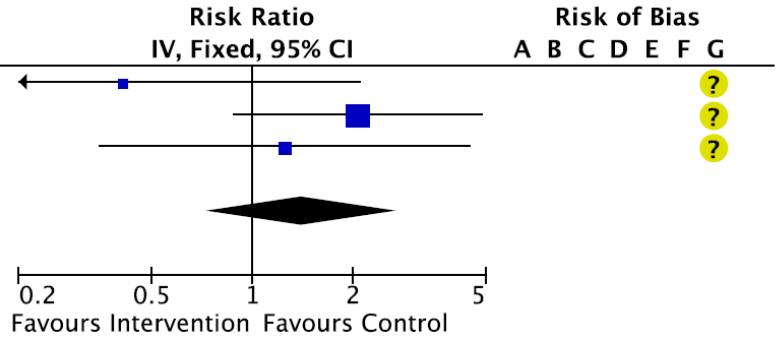


Question 10: sPTD < 34^{+0} weeks

Does metronidazole treatment of high risk pregnant women with BV and at any GA reduce the risk of PTD?
Outcome: sPTD < 34^{+0} weeks.

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Morales 1994 (1)	2	44	4	36	15.9%	0.41 [0.08, 2.11]	?
Odendaal 2002 (2)	17	70	6	51	58.0%	2.06 [0.88, 4.87]	?
Shennan 2009 (3)	4	8	2	5	26.1%	1.25 [0.35, 4.49]	?
Total (95% CI)		**122**		**92**	**100.0%**	**1.40 [0.73, 2.69]**	
Total events	23		12				

Heterogeneity: $Chi^2 = 2.98$, df = 2 (P = 0.23); $I^2 = 33\%$
Test for overall effect: Z = 1.01 (P = 0.31)



Footnotes
(1) Cochrane approved
(2) Cochrane approved
(3) Cochrane approved

Risk of bias legend
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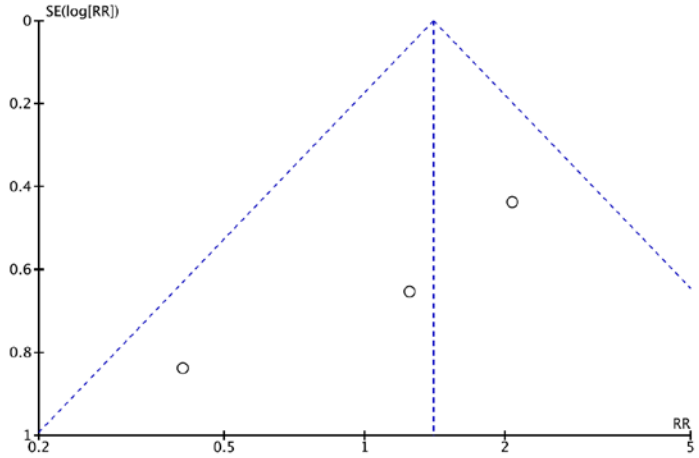
(**G**) Other bias


SE(log[RR])
0
0.2
0.4
0.6
0.8
1
RR
0.2
0.5
1
2
5

Clindamycin – clinical pharmacology

Writer: Agnes Ziobrowska-Bech

Pharmacology

Absorption of an oral dose clindamycin hydrochloride is virtually complete (90%). An average peak serum level of 2-3 mcg/mL is reached in 1 hour with a 150 mg oral dose. Concentrations of clindamycin in the serum increase linearly with increased dose. Serum levels exceed the MIC (minimum inhibitory concentration) for most indicated organisms for at least six hours following administration of the usually recommended doses. Clindamycin is widely distributed in body fluids and tissues (including bones). No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges. The average biological half-life is 2.4 hours. Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the feces; the remainder is excreted as bioinactive metabolites (70). Both the oral and topical use of clindamycin has been associated with severe colitis with the higher doses (70). This side effect does not appear to be more common nor does the pharmacokinetics of clindamycin appear to change during pregnancy (71, 72).

Clindamycin administered systemically crosses the placenta with umbilical cord serum concentrations up to 50% of the maternal serum concentration. Fetal tissue levels increase following multiple dosing with the drug concentrating in the fetal liver (71, 72). Clindamycin and its bioactive metabolites were demonstrated in the amniotic fluid and in fetal tissues when multiple doses were used. However, during pregnancies complicated by infection the distribution of clindamycin into the fetal compartment appears decreased based on increased protein binding (73).

The use of clindamycin treatment in pregnancy is registered as compatible (74). In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters, has not been associated with an increased frequency of congenital abnormalities (70). The Australian Drug Evaluation Committee's (ADEC) categorizes clindamycin as an A drug[i] (74). The U.S. Food and Drug Administration and the drug information leaflet categorizes clindamycin under Pregnancy Category B[ii] (All Trimesters) (70). Two recent reviews find that data are to limited to draw a conclusion about safety of clindamycin treatment in pregnant women (74, 75).

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (3.2 and 1.6 times the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (1.3 and 0.7 times the highest recommended adult human dose based on mg/m2, respectively) revealed no evidence of teratogenicity (70).

In a surveillance study of Michigan Medicaid, major congenital anomalies were reported in 31 (4.8%) of 647 infants whose mothers were given prescriptions for clindamycin during the first trimester of pregnancy (includes both maternal systemic and non-systemic administration). The expected frequency was 28 (4.3%). Specific data were available for six defect categories, including (observed/expected) 5/6 cardiovascular defects, 0/1 oral clefts, 1/0.5 spina bifida, 1/2 polydactyly, 0/1 limb-reduction defects, and 3/2 hypospadias. These data do not support an association between the drug and congenital defects (76).

The Swedish Medical Birth Registry holds data on 677 infants exposed to clindamycin (systemic administration) during early pregnancy. A total of 15 children had a malformation diagnosis (14 expected). No type of malformation was overrepresented and the frequency was expected (77).

Multiple clinical trials do not find an association with the use of clindamycin during pregnancy in the second and third trimesters and increased frequency of congenital malformations (34-37, 78-81).

Treatment with clindamycin appeared safe in a double-blind, placebo-controlled, randomized trial with 103 woman-perinate pairs. The efficacy, safety, and tolerance of a course of clindamycin (administered for 3 days intravenously and 4 days orally) among hospitalized women with preterm labor ≤ 34 weeks of gestation was evaluated (78).

In a randomized, double-blind, placebo-controlled trial, 104 women were treated with clindamycin 450 mg/day 6 weeks during their second and third trimester. There was no statistically significant difference in the rates of major or minor congenital malformations compared with placebo (clindamycin / placebo: 3.9% / 4.4%) (79).
In a clinical trial were 65 women were treated with oral clindamycin and quinine for malaria in the second or third trimester of pregnancy, the frequency of congenital anomalies was not increased (80).
In a randomized trial, 249 women with abnormal vaginal flora and vaginosis received clindamycin early in the second trimester (mean gestation of 15,6 weeks). The treatment consisted of clindamycin 300 mg twice daily for 5 days. Clindamycin treatment was found associated with a reduction in the incidence of late miscarriage and preterm births. No increase in the incidence of other adverse outcomes was noted, but the incidence of congenital anomalies was not the primary focus of the study (36).
In a prospective comparative study of pregnant women diagnosed as positive for bacterial vaginosis in the third trimester, 39 women were treated with vaginal clindamycin and 39 with oral clindamycin. There was a significant increase in birth weight values for oral clindamycin as compared with vaginal clindamycin. No adverse outcomes were noted among the children (81).
No adverse events attributable to treatment with clindamycin vaginal cream during the second trimester of pregnancy were observed among the infants of 178 women who participated in a clinical trial (34).
In a trial with 408 women diagnosed with bacterial vaginosis clindamycin vaginal cream therapy in the second trimester, was associated with significantly prolonged gestation in infants born preterm and reduced cost of neonatal care. No severe treatment-related adverse events were noted (35).
There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy (70).
No malformations were observed among the children of 16 women who were treated with 500 mg amoxicillin and 300 mg clindamycin 3 times a day for ≥ 7 days in the first trimester of pregnancy to prevent recurrent miscarriage (37).
Clindamycin solutions for injection contain benzyl alcohol which can cross the placenta and is associated with increased rates of mortality and morbidity in premature infants (82, 83).

Conclusion

Clindamycin administered systemically crosses the placenta. A causal relationship between clindamycin and teratogenic effects has not been found and the use of clindamycin treatment in pregnancy is registered as compatible (category B (A) drug).
Reproduction studies performed in rodents revealed no evidence of teratogenicity.
Surveillance studies of infants exposed to clindamycin during early pregnancy / first trimester do not support an association between the drug and congenital defects. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Clindamycin should be used during the first trimester of pregnancy only if clearly needed.
In clinical trials with pregnant women, the systemic or vaginal administration of clindamycin during the second and third trimester has not been associated with an increased frequency of congenital abnormalities.
Benzyl alcohol, which is an ingredient in clindamycin solutions, is associated with increased rates of mortality and morbidity in premature infants.

Metronidazole – clinical pharmacology

Writer: Agnes Ziobrowska-Bech

Metronidazole is bactericidal, amoebicidal and trichomonacidal. The exact mode of action has not been fully elucidated. The metabolites appear to be responsible for the cytotoxic and antimicrobial effects of the drug which include disruption of DNA and inhibition of nucleic acid synthesis (84).

Pharmacology

Maximum concentrations occur in serum 1 to 2 hours after oral administration (T_{max}) and at the end of the infusion after intravenous administration. The systemic bioavailability is 80%. The biological half-life is approximately 6 to 8 hours. When administered in suppository form, metronidazole is absorbed slowly and less completely than oral tablets. Metronidazole blood levels are significantly lower after administration vaginally than those achieved with oral metronidazole. The bioavailability when administered vaginally is 20 % for tablets and 56% for gel. The topical T_{max} is 8-12 hours (85, 86).

Metronidazole is widely distributed in body tissues and fluids. It diffuses across the blood-brain barrier, crosses the placenta and is found in the breast milk of nursing mothers in concentrations equivalent to those in serum. Metronidazole is not significantly bound to plasma protein. Most of the dose is excreted in the urine as metronidazole and its metabolites (86).

The manufacturer considers metronidazole to be contraindicated during the 1st trimester of pregnancy as it crosses the placenta and enters fetal circulation rapidly (86).

The use of metronidazole for trichomoniasis or vaginosis during the 2nd and 3rd trimesters is acceptable. For other indication, metronidazole can be used during pregnancy if there are no other alternatives with established safety profiles (73).

The U.S. Food and Drug Administration categorizes clindamycin under Pregnancy Category B. The Australian Drug Evaluation Committee's (ADEC) and the drug information leaflet categorizes metronidazole as an B2 drug (85). *

Experimental studies have shown that metronidazole is mutagenic in bacteria and carcinogenic in rodents involving chronic oral administration (86). Although these properties have never been shown in humans, concern for these toxicities have led some to advise against the use of metronidazole in pregnancy (86, 87). However, no association with human cancer has been proven (85). (2-4)

A case report from 1995 described a child with adrenal neuroblastoma with hepatic metastatis born by a woman treated with metronidazole, orally and intravaginally, during the 1st trimester. A casual relationship between the tumor and metronidazole could not be established (88).

An epidemiologic study that matched the possible use of at metronidazole prescription at any time during gestation and the incidence of neoplastic disease in children up to the age of 5 years (N=175) did not find any statistically significant elevated risk of any form of cancer in the study population . However, the authors stated that the increased risk of neuroblastoma (RR 2, 60 , 95% CI 0,89-7,59) needed further evaluation (89).

Metronidazole has not been shown to be teratogenic in either human or animal studies (86).

There are some case reports of holotelenchepaly, clefts in the soft and hard palate and optic atrophy in infants whose mothers had been taking metronidazole during the 1st trimester (90).

However, most studies, case reports, and reviews have described the safe use of metronidazole during pregnancy (all trimesters) and data exists for several thousand 1st trimester exposed children without an increased teratogenic risk (90-93).

The Swedish Medical Birth Registry holds data on 668 infants exposed to metronidazole (systemic administration) during early pregnancy. A total of 11 children had a malformation diagnosis (14 expected). No type of malformation was overrepresented (77).

Conclusion

- Metronidazole administered systemically crosses the placenta and enters fetal circulation rapidly.
- Most of the published evidence suggests that metronidazole therapy during pregnancy, including the first trimester, does not lead to congenital malformations.
- At present, it is not possible to assess the risk to the fetus from the carcinogenic potential of metronidazole.

- The use of metronidazole for trichomoniasis or vaginosis during the 2nd and 3rd trimesters is acceptable. For other indications, metronidazole can be used during pregnancy if there are no other alternatives with established safety profiles.

Pregnancy risk categories

- Australian Drug Evaluation Committee's (ADEC) Category: B2 (Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).)
- U.S. Food and Drug Administration's Pregnancy Category: B (Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.)

Clindamycin - microbiologicy

Writer: Claus Østergaard

Clindamycin belongs to the antibiotic class of lincosamides. Its mechanism of action is inhibition of the bacterial protein synthesis by a reversible binding to the 50S subunit of the bacterial ribosome.

Clindamycin is active against most Gram-positive bacteria, including streptococci and staphylococci, but enterococci are inherently resistant. Acquired resistance amongst streptococci are rarely seen in Denmark, and is still uncommon in *Staphylococcus aureus*, apart from in some MRSA-strains.

Most anaerobic bacteria are naturally susceptible to Clindamycin. Thus clindamycin is active against Gram-positive anaerobes, like *Clostridium, Peptostreptococcus, Propionibacterium and Lactobacillus spp*. but *Clostridium difficile* is an important exception. Gram-negative anaerobes, including *Bacteroides, Fusobacterium, Prevotella and Mobiluncus spp.* are likewise naturally susceptible to clindamycin.
In addition Clindamycin has good activity against the microaerophilic Gram-variable *Gardnerella vaginalis*.
In contrast Clindamycin has no therapeutic activity neither against facultatively anaerobic Gram-negative rods, including the *Enterobacteriaceae* , e.g. *E. coli, Klebsiella spp.*, nor the aerobic Gram-negative rods, such as *Pseudomonas* and *Acinetobacter spp.* .

In regard to the antibacterial spectrum of clindamycin it is important to notice that acquired resistance is already common amongst the anaerobes, also in Denmark. Generally bacteria easily acquire resistance to clindamycin, and it is well documented that resistance develop even in the course of a single treatment of bacterial vaginosis with clindamycin. Therefore increased use of clindamycin in a population will most likely lead to significant decreased therapeutic efficacy of the drug.

Ecological effects concerning use of clindamycin

Systemic administered clindamycin greatly affects the normal human microbiome (normal flora), it being in the gastrointestinal tract, the airways, on the skin, or in the vagina. Probably as a consequence of this great disturbing effect on the gastrointestinal flora, anorexia, nausea, vomiting, abdominal pain, flatulence, bloating, constipation and diarrhoea, is very common adverse effect when using oral clindamycin. Clindamycin is also notoriously know for its ability to induce infection in the colon by endospore forming toxigenic *Clostridium difficile*, which may in worst cases develop into pseudomembraneus colitis and perforation of the colon. Clindamycin is usually regarded as one on the three antibiotics with the greatest tendency to induce

C. difficile-colitis, as is the fluoroquinolones and third generation cefalosporines. These infections are often recurrent in spite of treatment with oral vancomycin or metronidazole, especially amongst patients with cancer getting chemotherapy, patients undergoing abdominal surgical procedures and patients with comorbidities.

Therapy with clindamycin often leads to superinfections caused by yeast, e.g. vaginal and oral candidiasis. Disruption of the normal vaginal flora can also lead to nonspecific vaginitis and vulvuvaginitis with symptoms like local pain, vaginal discharge and mucosal ulceration. These adverse effects are seen in almost 10 % of non-pregnant and even more often in pregnant women.

Topical vs. systemic use of clindamycin
If clindamycin is to be used for treating bacterial vaginosis, topical rather than systemic clindamycin should be preferred, since BV is a local condition is in the vaginal mucosa, and because systemic clindamycin causes more harmful ecological effects. Be noted that in some cases topical vaginal use of clindamycin can lead to significant systemic absorption.

Metronidazol - microbiology

Writer: Claus Østergaard

Metronidazole is a nitroimidazole, and actually a prodrug that is activated by reduction inside anaerobic bacteria and some anaerobic parasites. The mechanism of action is only partly known, but the activated drug binds the microbial DNA and causes inhibition of DNA-synthesis. Metronidazole can also be activated by an alternative way in some microaerophilic organism's, like *Helicobacter pylori*. Metronidazole is metabolised in the liver into partly therapeutically active metabolites.

Metronidazole is active against most obligate anaerobic bacteria, Gram-positives like *Clostridium spp.* including *C. difficile*, and *Peptostreptococcus spp*. as well as Gram-negatives, e.g. *Bacteroides, Fusobacterium, Prevotella spp*. The activity against the microaerophilic *Gardnerella vaginalis* is more uncertain but some of the metabolites are more active against this organism. Some *Mobiluncus spp*. are susceptible, but many are not.

Aerotolerant anaerobes such as *Propionibacterium, Bifidobacterium*, and *Lactobacillus spp*. are less susceptible and usually resistant.

Microorganisms do not readily develop resistance and acquired resistance is generally uncommon in spite of its broad use since mid 1950s.

Ecological effects concerning use of metronidazole
Although metronidazole is active against most of the anaerobic bacteria that make up the majority of the microbiome in the gastrointestinal tract, the negative ecological consequences are regarded as relatively small compared to use of systemic clindamycin. Infections by *Clostridium difficile* induced by metronidazole are only anecdotally reported and metronidazole is one of the two preferred drug for treating *C. difficile*-infections. Vaginal candidiasis is a common (1-10%) adverse effect of topical vaginal use of metronidazole.

Topical vs. systemic use of metronidazole

Since the harmful ecological effects metronidazole is considerably less compared to clindamycin, the overall advantage of using topical over systemic metronidazole is not obvious. This holds true as long as the treatment length is short (no more than a week) and risk of especially neurological adverse effects of systemic treatment is negligible.

The microbiological comparison of clindamycin vs. metronidazole

Considering the commonness of bacterial vaginosis and the benign nature of the condition, it is very important that the recommended first choice of antibiotic is one that has as few ecological consequences as possible and one that defies development of resistance the most. From a clinical microbiological viewpoint it seems very risky to advocate the routine use of clindamycin for treating BV. If an antibiotic is indicated in treating a patient with of bacterial vaginosis, metronidazole should be the drug of first choice.

Probiotics – background

Writer: KS & RBH

Vaginal vs. oral administration.

Oral as well as vaginal administration of probiotics to non-pregnant women (used alone or in combination with antibiotics) is beneficial for treating and preventing BV when compared with placebo (94, 95). The vaginal administration allows a smaller dosage and less frequent administration and may be more effective than the oral route (95), whereas the oral administration is more convenient (94, 95).

Strain of probiotic

Concerning BV in non-pregnant women, *L.Rhamnosus GR-1, L. Acidophilus and L. Fermentum RC-14* appear to be the most beneficial (94, 95).

Dietary studies

Probiotic yogurt has positive effects on digestion (96) when the number CFUs exceeds 1 billion (Gudrun Weiss, Department of Basic Sciences and Environment, Molecular Immunology, Faculty of Life Sciences, University of Copenhagen, Frederiksberg, Denmark (97). Yogurts that advertise the addition of active probiotics most often label the strain of probiotic but less often with the quantity. Probiotic viability is negatively affected by heat and exposure to other ingredients in the yogurt, although each probiotic strain has its own tolerance threshold.

Table. Probiotic supplement for treatment of BV available in Danish pharmacies

Vaginal supplements

Product	**Pharmaceutical form**	**Mikro-Organism**	**Total**	**CFU* pr unit**	**Daily dosis**	**Treatment Period**	**Price DDD (EURO)**
Gynolact	Vaginal tablet	L.Acidophilus L.Casei L.Rhamnosus	3	2×10^9	1 vaginal tablet before sleep	7 days	1.07
VivagPlus	Vaginal capsule	L. Gasseri L.Rhamnosus	1	2×10^9	1 vaginal cap-sule Before sleep	6 days	1.61

Vivag	Vaginal capsule	L.Acidophilus	1	10^9	1 vaginal capsule	2 times a day for 6 days	2.60
Oral supplement							
Product	**Pharmaceutical form**	**Mikro-Organism**	**Total**	**CFU* pr unit**	**Daily dosis**	**Treatment Period**	**Price DDD (EURO)**
Femidur	Oral tablet	L.Rhamnosus L. Reuteri	2	5×10^9	1 tablet dagligt Oralt	10 days	1.32
Lacto Lady***	Oral tablet	L.Acidophilus L. Casei L.Rhamnosus B. Longum	4	4×10^9	1 tablet 2 times daily	NA	30 tablets 15.99
Lacto-Seven****	Oral	L.acidophilus L. casei L. plantarum L.reuteri L.rhamnosus B.longum Streptococcus thermophilus	7	7×10^9	1 tablet 2 times daily	NA	100 tablets 26,00
Yogurt							
Product	**Pharmaceutical form**	**Mikro-Organism**	**Total**	**CFU* pr unit**	**Daily dosis**	**Treatment Period**	**Price DDD (EURO)**
Cultura	Yogurt	L.Acidophilus L. Casei B.BB12	3	NA	100 mg 2 times a day (2)*****	NA	0.53
Actimel	Yogurt	L. Casei	1	NA	100 mg 2 times a day (2)*****	NA	1.27
A38	Yogurt	L.Acidophilus	1	NA	100 mg 2 times a day (2)*****	NA	0.44

* CFU: colony forming units

**Note that prices are not calculated in cures, since the customer still need to buy a whole package
*** Intended for treatment of urinary tract infection. Does also contain 800 mg cranberry extract
**** Intended for treatent of gastrointestinal symptoms. Wide variety of similar products available
***** based on one reference (2).

Supplement: Search protocol 1

Writer: AE

This search was conducted by Berit Elisabeth Alving

Præmatur fødsel	Komplikation	Intervention/behandling	Tidsbegænsning	Sprog
Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion	vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis	clindamycin OR metronidazole OR amoxicillin OR erythromycin	De sidste 10 år 2004-2014	Dansk, engelsk, norsk Svensk fransk tysk

Do	DO	Antibiotic OR Antibiotics	2013-14	Do.
Do	DO	Probiotic OR probiotics	2010-14	Do.
Do	DO	DO	De sidste 15 år	Kun skandinaviske studier Kun fra WoS

Søgninger i: Pubmed, Embase, Cochrane, WoS

Pubmed History

Search	Query	Items found
#4	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin)	309
#11	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years; English; Danish; French; Norwegian; Swedish; German	112

Search	Query	Items found
#10	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years; English; Danish; French; Norwegian; Swedish	112
#9	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years; English; Danish; French; Norwegian	112
#8	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years; English; Danish; French	112
#7	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years; English; Danish	110
#6	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR	110

Search	Query	Items found
	Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years; English	
#5	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND (clindamycin OR metronidazole OR amoxicillin OR erythromycin) Filters: published in the last 10 years	117
#3	Search clindamycin OR metronidazole OR amoxicillin OR erythromycin	60710
#2	Search vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis	12418
#1	Search Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion	487952

03.10.2014

Pubmed history

Search	Query	Items found
#42	Search (((Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis)) AND ((Antibiotic OR Antibiotics) AND ((English[lang] OR Danish[lang] OR French[lang] OR Norwegian[lang]	17

Search	Query	Items found
	OR Swedish[lang] OR German[lang]))) Filters: Publication date from 2013/01/01 to 2014/12/31; English; Danish; French; Norwegian; Swedish; German	

03.10.2014 Antibiotic 2013-14

Pubmed History

Search	Query	Items found
#46	Search (((Probiotic OR probiotics)) AND (Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion)) AND (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis) Filters:Publication date from 2010/01/01 to 2014/12/31; English; Danish; French; Norwegian; Swedish; German	28

03.10.2014 + probiotics 2010-14

Web of Science

Results: 13

(from Web of Science Core Collection)

You searched for: TOPIC:(Premature OR Preterm OR Early preterm OR Very preterm OR Preterm birth OR Premature birth OR Premature Labor OR Premature Labour OR Preterm Labor OR Preterm Labour OR Premature Obstetric Labor OR Premature Obstetric Labour OR Extremely Premature Infant OR Extremely Preterm Infant OR Neonatal Prematurity OR Prematurity OR Preterm delivery OR obstetrics OR obstetric OR Late miscarriage OR Perinatal mortality OR Perinatal Mortalities OR Perinatal morbidity OR abortion) *AND* TOPIC: (vaginitis OR vaginosis OR vaginitides OR bacterial vaginitis OR bacterial vaginosis OR bacterial vaginosis OR bacterial vaginitis) *AND* TOPIC: (clindamycin OR metronidazole OR amoxicillin OR erythromycin)

Refined by:COUNTRIES/TERRITORIES: (FINLAND OR SWEDEN OR DENMARK OR NORWAY)

Timespan: 1999-2014. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

03.10.2014

Embase Search History

# ▲	Searches	Results
1	(Premature or Preterm or Early preterm or Very preterm or Preterm birth or Premature birth or Premature Labor or Premature Labour or Preterm Labor or Preterm Labour or Premature Obstetric Labor or Premature Obstetric Labour or Extremely Premature Infant or Extremely Preterm Infant or Neonatal Prematurity or Prematurity or Preterm delivery or obstetrics or obstetric or Late miscarriage or Perinatal mortality or Perinatal Mortalities or Perinatal morbidity or abortion).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	361300
2	exp prematurity/	70211
3	exp premature labor/	29189
4	exp perinatal mortality/	16332
5	exp perinatal morbidity/	8644
6	1 or 2 or 3 or 4 or 5	366859
7	(vaginitis or vaginosis or vaginitides or bacterial vaginitis or bacterial vaginosis or bacterial vaginosis or bacterial vaginitis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	12120
8	exp vaginitis/	11635
9	(clindamycin or metronidazole or amoxicillin or erythromycin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	171307
10	exp clindamycin/	37032
11	exp metronidazole/	50025
12	exp amoxicillin/	46381
13	exp erythromycin/	59499
14	7 or 8	13410
15	9 or 10 or 11 or 12 or 13	171307
16	6 and 14 and 15	550
17	limit 16 to ((danish or english or french or norwegian or swedish) and yr="2004 -Current")	293

03.10.2014

Embase Search History

18	(Antibiotic or Antibiotics).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	518632
19	exp antibiotic agent/	944117
20	18 or 19	1083631
21	6 and 14 and 20	731
22	limit 21 to yr="2013 -Current"	54
23	limit 22 to (danish or english or french or norwegian or swedish)	53

03.10.2014 +Antibiotic 2013-14

Embase Search history

24	(Probiotic or probiotics).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20709
25	exp probiotic agent/	17806
26	24 or 25	20709
27	6 and 14 and 26	55
28	limit 27 to ((danish or english or french or norwegian or swedish) and yr="2010 -Current")	27

03.10.2014 + probiotics 2010-14

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		Obstetric Labour or Extremely Premature Infant or Extremely Preterm Infant or Neonatal Prematurity or Prematurity or Preterm delivery or obstetrics or obstetric or Late miscarriage or Perinatal mortality or Perinatal Mortalities or Perinatal morbidity or abortion:ti,ab,kw (Word variations have been searched)	
#2	vaginitis or vaginosis or vaginitides or bacterial vaginitis or bacterial vaginosis or bacterial vaginosis or bacterial vaginitis:ti,ab,kw (Word variations have been searched)	S	945
#3	clindamycin or metronidazole or amoxicillin or erythromycin:ti,ab,kw (Word variations have been searched)	S	7938
Edit #4	#1 and #2 and #3 Publication Year from 2004 to 2014		28

All Results (28)

- Cochrane Reviews (3)
  - All
  - Review
  - Protocol
- Other Reviews (2)
- Trials (23)
- Methods Studies (0)
- Technology Assessments (0)
- Economic Evaluations (0)
- Cochrane Groups (0)

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#1	Premature or Preterm or Early preterm or Very preterm or Preterm birth or Premature birth or Premature Labor or Premature Labour or Preterm Labor or Preterm Labour or Premature Obstetric Labor or Premature Obstetric Labour or Extremely Premature Infant or Extremely Preterm Infant or Neonatal Prematurity or Prematurity or Preterm delivery or obstetrics or obstetric or Late miscarriage or Perinatal mortality or Perinatal Mortalities or Perinatal morbidity or abortion:ti,ab,kw (Word variations have been searched)	S	19042
#2	vaginitis or vaginosis or vaginitides or bacterial vaginitis or bacterial vaginosis or bacterial vaginosis or bacterial vaginitis:ti,ab,kw (Word variations have been searched)	S	945
#3	clindamycin or metronidazole or amoxicillin or erythromycin:ti,ab,kw (Word variations have been searched)	S	7938
Edit #4	#1 and #2 and #3 Publication Year from 2004 to 2014		28
#5	Antibiotic or Antibiotics:ti,ab,kw (Word variations have been searched)	S	15152
Edit #6	#1 and #2 and 5 Publication Year from 2013 to 2014		5

+ Antibiotics 2013-14
1 review og 4 trials.
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#1	Premature or Preterm or Early preterm or Very preterm or Preterm birth or Premature birth or Premature Labor or Premature Labour or Preterm Labor or Preterm Labour or Premature Obstetric Labor or Premature Obstetric Labour or Extremely Premature Infant or Extremely Preterm Infant or Neonatal Prematurity or Prematurity or Preterm delivery or obstetrics or obstetric or Late miscarriage or Perinatal mortality or Perinatal Mortalities or Perinatal morbidity or abortion:ti,ab,kw (Word variations have been searched)	S	19042
#2	vaginitis or vaginosis or vaginitides or bacterial vaginitis or bacterial vaginosis or bacterial vaginosis or bacterial vaginitis:ti,ab,kw (Word variations have been searched)	S	945
#3	clindamycin or metronidazole or amoxicillin or erythromycin:ti,ab,kw (Word variations have been searched)	S	7938
Edit #4	#1 and #2 and #3 Publication Year from 2004 to 2014		28
#5	Antibiotic or Antibiotics:ti,ab,kw (Word variations have been searched)	S	15152
Edit #6	#1 and #2 and 5 Publication Year from 2013 to 2014		5
#7	Probiotic or probiotics:ti,ab,kw (Word variations have been searched)	S	1923
Edit #8	#1 and #2 and #7 Publication Year from 2010 to 2014		3

3 trials
03.10.2014

Supplement: Litterature search protocol 2
Conducted by
BV

	# ▲	Searches	Results	Search Type	Actions
☐	1	("preterm labor" or "preterm labour" or "preterm birth" or "preterm delivery" or foedsel).af.	24597	Advanced	Display More ≫
☐	2	(vaginosis or infection* or bacterial or bakteriel*).af.	2298861	Advanced	Display More ≫
☐	3	1 and 2	4915	Advanced	Display More ≫
☐	4	limit 3 to (yr="2004 -Current" and (danish or english or norwegian or swedish))	3110	Advanced	Display More ≫
☐	5	limit 4 to humans	2631	Advanced	Display More ≫
☐	**6**	**limit 5 to "review"**	**465**	**Advanced**	Display More ≫

5-8-2014

Update February 2019

The guideline entitled **"Bacterial vaginosis in pregnancy and risk of spontaneous preterm delivery"** was approved by the Danish Society of Obstetrics and Gynecology (DSOG) in January 2015 and later published on both the DSOG and NFOG websites, including an extract published in Acta Obstetricia et Gynecologica Scandinavica in May 2016 (1). Since the publication, some Obstetricians have criticized the guideline both at the time of publication and again in 2018 (2,3) and especially the inclusion of the results of a conference abstract published by Subtil et al. in 2014 (4). Although this critique was evaluated already in 2016 and did not lead to any changes in the original guideline (5), we are now urged to make an update of our guideline as Subtil et al. recently published their results in Lancet in November 2018 (6).

Subtil et al. 2018 conducted a huge study (84,520 pregnant women screened, 2,869 randomized), looking into the effect of early clindamycin treatment (one or three courses as intervention arm) compared to placebo to prevent very preterm birth <32 weeks and late miscarriage as primary outcome in low risk women (Median gestational age at inclusion 12.4 weeks (SD2.1)). For the primary outcome mentioned, the intention-to-treat analysis found no significant effect: 1.10 (0.53–2.32); p=0.82. For spontaneous preterm delivery (sPTD) <37 weeks, they found no significant effect: 1.17 (0.81–1.69); p=0.40. In fact, both effect estimates favored the placebo arm. The only significant effect observed in the entire study was increased side effects in the intervention arms such as diarrhea (P=0.0071) and abdominal pain (P=0.034). Per protocol analysis yielded similar results, albeit the only significant finding was an average of 5 fewer days hospitalized after PPROM or PROM in the intervention group as compared to placebo (P=0.020). Pregnant women at high risk of sPTD (N=236) were randomized to either one course of clindamycin or three courses of clindamycin – no placebo arm. The sub-analysis found no significant effect in neither primary nor secondary outcome (6).

The updated meta-analysis of our guideline (including Subtil et al. 2018) did not change the effect estimates previously reported regarding overall spontaneous preterm delivery <37 weeks and in women included early (<20weeks) and randomized to clindamycin treatment. However, the GRADE quality of evidence is now moderate and not low as we graded down for the inclusion of abstract results. Hence, after the publication of the large RCT by Subtil et al. 2018, we now upgrade the overall recommendation from advising against clindamycin treatment to recommending against treatment of BV with clindamycin to reduce spontaneous preterm delivery.

We have not made any other updates than incorporating the study by Subtil et al. (2018) into our guideline.

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6. Subtil D, Brabant G, Tilloy E, Devos P, Canis F, Fruchart A, et al. Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial. Lancet Lond Engl. 2018 17;392(10160):2171–9.

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[i] Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
[ii] Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.