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EXPERT OPINION

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Treatment of bacterial vaginosis: what we have and what we miss

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Introduction: The disturbing, foul-smelling discharge of bacterial vaginosis (BV) is a nuisance to women. Treatment possibilities for BV are limited and only achieve complete cure in 65 to 85% of cases. In most women, the condition relapses within weeks to months after treatment.

Areas covered: In search of new therapeutic actions to cure, prevent or delay recurrences of BV, PubMed and web of science were searched for papers with i) decent study layout, ii) proper statistics, iii) comparison group (placebo or standard treatment) and iv) language English, French, Dutch or German. The following keywords were used: bacterial vaginosis and treatment or management or therapy or prophylaxis or prevention. Results were grouped in treatment categories and were discussed.

Expert opinion: Clindamycin and metronidazole are the standard drugs for BV. As other antibiotic and acidifying treatments are progressively being studied, like tinidazole, rifaximin, nitrofurantoin, dequalinium chloride, vitamin C and lactic acid, more options have become available for switching therapy, combining therapies and long-term prophylactic use to prevent recurrences. Further studies are needed. Also, adjuvant therapy with probiotics may have a significant role in improving efficacy and in preventing recurrences. However, it is unlikely that probiotics will replace antibiotherapy.

Keywords: abnormal vaginal flora, aerobic vaginitis, prophylaxis, recurrent vaginitis

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1. Introduction

Abnormal vaginal discharge can be caused by non-infectious causes, cervicitis, *Candida*, *Trichomonas vaginalis*, bacterial vaginosis (BV) and/or aerobic vaginitis (AV). There is only one single symptom of BV: foul-smelling discharge. This causes some women to stop functioning in social and sexual life: they sense the smell, think everybody else senses it, including the sexual partner, causing a feeling of dirtiness and being unattractive and unhygienic [1]. At the same time, there are women with BV who seem to be undisturbed by the condition. Typically, when diagnosing it at the occasion of a routine checkup with Pap smear, these women will deny any discharge or smell, even while, at times, it is obvious to the physician. As a definition, the latter are called 'asymptomatic BV', although one wonders whether the discerning ability of a patient to recognize a disease status is enough reason to call a condition 'asymptomatic'.

The most typical symptoms of BV (watery, superfluous gray discharge and the typical fishy smell) can be confirmed by an increased vaginal pH (> 4.7) and a typical microscopy: granular flora, with so many bacteria on the epithelial cells (clue cells) and in between them that it is impossible to count them as they are so numerous and overlay each other. This is distinct from the findings in AV, where bacteria are much less numerous and more readily identified as single organisms. Bacterial morphotypes are easier to discern and recognize and are more prominent than anaerobic bacteria [2]. Also in AV, an inflammatory response is usually seen

Article highlights.

- In order to provide successful treatment in patients with vulvovaginal symptoms, a refined and complete diagnosis of the vaginal microflora abnormalities is warranted. For this, detailed microscopic analysis is obligatory.
- Per-oral or vaginally applied metronidazole or clindamycin are equally efficacious treatments and are considered standard of treatment. However, no > 60 to 85% therapeutic cure rates are claimed after 1 month.
- New antibiotic and antiseptic drugs are being tested, such as vaginal rifaximin, vaginal or oral nitrofurantoin and vaginal dequalinium chloride, with cure rates similar to the standard treatment. Further studies are needed, but alternatives of combination therapies become a future option.
- Probiotics seem to be potentiating the effect of antibiotics in the treatment of BV (adjuvant therapy) and may be able to prevent, postpone or reduce relapses after initial antibiotic treatment.
- In pregnancy, clindamycin seems to be a superior drug for treatment of women with BV and other forms of abnormal vaginal bacterial microflora and is preferred above metronidazole.

This box summarizes key points contained in the article.

with numerous leukocytes that can have a toxic appearance, and even epithelial cells from the parabasal type.

Other symptoms, like itching, abdominal pain, dyspareunia, irritation and redness are not the symptoms of BV, unless it is a combined infection of BV with AV, *Candida*, or *T. Vaginalis* is present. One has to be very careful not to miss such infections, as the treatment of BV will not improve these symptoms, and may, in fact, actually worsen them.

2. Etiology and transmission

BV can best be described as an 'ecological disaster' of the vaginal microflora. The normal flora which is predominantly composed of lactobacillary morphotypes is replaced by a 100- to 1000-fold higher number of mainly anaerobic bacteria. Although sporadic occurrence of the disease occurs, the majority of patients suffer from chronic or recurrent symptoms. Although not completely fitting the diagnosis of 'sexually transmitted infection' (STI), BV is strongly associated with sexual activity. Women having sex with women share similar lactobacillary types and are at increased risk of BV [3]. Heterosexual transmission is thought to occur, as demonstrated by the presence of penile clue cells, finding biofilm fragments in male urine and sperm [4,5] and BV-associated bacteria in sperm and prostate fluid [6,7], but in clinical trials with treatment of males, remission could not be achieved in women with recurrent BV [8].

BV is typically encountered in women of childbearing age, rarely during menopause, but never in children. In Caucasian

women, the prevalence is 5 – 15% in Western Europe, but seems to be higher in African and American blacks [9-16]. Although about half of women with BV have no symptoms, and the only symptom of uncomplicated BV is a foul-smelling discharge, there is an association with posthysterectomy vaginal cuff infection [17-19], post-abortion endometritis [20-24], increased risk of acquiring STI, especially genital herpes and HIV [25-33], increased risk of spontaneous miscarriage ranging between 13 and 24 gestational weeks [32-36] and preterm birth [37-51].

3. Diagnosis and differential diagnosis

Most pathognomonic diagnostic sign is the presence of a foul, fishy smell, which is encountered when performing a speculum exam ('sniff test'), or after adding one droplet of 10% KOH to the wet mount slide ('whiff test').

The clinical suspicion is always best confirmed by microscopic examination of the vaginal fluid. Whenever possible, wet mount phase contrast microscopy should be applied [52,53]. This allows differentiation between more subtle forms of abnormal vaginal flora such as full-blown BV, partial BV, AV and mixed infections with BV [54]. If BV overtakes the normal flora, leading to complete replacement of the lactobacillary flora by anaerobic morphotypes, and covers > 20% of epithelial cells with bacteria (clue cells), it is called full-blown BV. In a transitional state, both BV flora patterns, composed of granular, anaerobic bacteria and normal lactobacillary dominant areas coincide. Hence, likelihood to have more than a few clue cells is low, and this transitional condition is called 'partial BV' [2]. AV is a condition of abnormal vaginal flora which is completely different from BV: although both conditions have a depression of lactobacilli, low vaginal lactate [55,56] and increased pH in common, the microflora type with aerobic cocci and/or small bacilli in AV is completely different from the granular anaerobic flora in BV, and the latter typically lacks the presence of immune response (vaginal leukocytes) and microscopic signs impairment of the vaginal epithelium (presence of parabasal cells) that the former expresses [2].

If immediate examination is not possible, the swab can be sent to the laboratory for a Gram stain to confirm the diagnosis of BV by applying the Nugent's or Hay-Ison score [57-59]. In the most commonly used system according to Nugent, based on the semiquantitative number of lactobacillary, *Gardnerella* or *Mobiluncus* morphotypes, a score of 1 – 3 corresponds to normal flora, a score of 4 – 6 to 'intermediate flora' and a score of 7 – 10 to BV. Pap smears, bacterial cultures or NAAT techniques are suboptimal, expensive or too time-consuming and should not be used to detect BV in clinical samples in the routine setting [60,61].

Based on the amines produced in BV, its increased vaginal pH, the microbial constituents as picked-up by nuclear acid amplification tests and the different morphological patterns on microscopy, several diagnostic tests have been developed

and commercialized, but in most circumstances, microscopy and clinical examination suffice for a proper diagnosis [67-74].

4. Therapy

The cornerstone of the treatment is the use of local or systemic antibiotics with activity against anaerobes. Besides these, antiseptic or probiotic preparations can be used, the latter more in an adjuvant or prophylactic setting (Table 1).

4.1 Antibiotics

At present, three antibiotics are approved for treatment of BV: metronidazole, tinidazole and clindamycin. These drugs have a similar efficacy when given locally in the vagina or taken orally and have cure rates of about 58 to 92% after 1 month in doses of 500 mg oral metronidazole twice daily for 5 days, 2% vaginal clindamycin cream once daily for 7 days, oral clindamycin 300 mg twice daily for 7 days, metronidazole 0.75% vaginal gel once daily for 5 days or the stat regimens of 2 g of metronidazole or tinidazole in a single dose [75-85]. None of the 5-nitro-imidazoles (tinidazole, metronidazole, ornidazole, secnidazole) was superior to the other (cure rates 57 – 63%) after 1 month, but the combination of vaginal plus oral use was somewhat superior: 80 – 86% cure rates vs 75 – 86% [86-90]. Using a high stat dose of 2 g of metronidazole vaginally proved as efficacious as 2 g orally, but it produced few side effects [91]. In general, for both metronidazole and clindamycin, the local formulations showed equal efficacies than oral route (75 – 86%), but few side effects were noted [92,93].

Other antibiotics like ofloxacin, azithromycin or erythromycin should not be used to treat BV [94-96], although cefadroxil had comparable cure rates to metronidazole in one study [97]. Some data indicate that more aggressive BV treatment with antibiotics (2% clindamycin vaginal cream together with oral clindamycin 600 mg/day 7 days, followed with vaginal metronidazole gel for 5 days) combined with specific *Lactobacillus* strain and partner treatment can provide long-lasting cure in some cases [98]. However, the doses used in this trial were non-conformistic and suprathapeutic and cannot be advised for uncomplicated cases.

Side effects like nausea, pyrosis, stomach pains, intolerance for alcohol due to metronidazole [99] and the weakening effect on the condoms [100,101] and the rare but severe complication of pseudomembranous colitis [102] due to clindamycin, warrant caution for excessive use of these drugs, as well as the increasing development of antibiotic resistance [103-108].

An innovative approach was to test a locally applied non-absorbable, non-imidazole antibiotic, rifaximin, in the vagina of women with BV. Rifaximin, a derivative of rifamycin, with broad-spectrum antibacterial activity covering gram-positive, gram-negative, aerobic, and anaerobic bacteria has been used to treat gastrointestinal infections as an oral formulation and, being negligibly absorbed, presents a good safety profile [109]. Four different regimens were tested and compared

to placebo showing that rifaximin 25 mg/day for 5 days is the most effective treatment to be used in future pivotal studies for the treatment of BV [110]. Quantitative polymerase chain reaction (PCR) demonstrated an increase of *Lactobacillus* genus and a decrease of the BV-related bacterial groups after the antibiotic treatment. PCR-denaturing gradient gel electrophoresis (DGGE) profiles confirmed the capability of rifaximin to modulate the composition of the vaginal microbial communities and to reduce their complexity [111]. In a study comparing women with BV using rifaximin versus normal control women, it was demonstrated that a large number of human proteins were differentially expressed in women with BV in comparison with healthy women (n = 118) and in BV-affected women treated with rifaximin (n = 284) [112]. In both comparisons, approximately 20% of the dysregulated proteins were involved in the innate immune response. Of the 24 proteins, 21 increased in abundance in women with BV versus healthy women and 31 of 59 proteins decreased after rifaximin treatment, thus suggesting a general reduction of the immune response resulting from the therapy. Major changes in protein abundance were found following treatment with 25 mg/day of rifaximin for 5 days.

4.2 Antiseptics

Antiseptics have antibacterial actions against a wide range of aerobic and anaerobic bacteria, by nonspecifically disrupting the bacterial cells membrane. Antiseptics like benzydamine, chlorhexidine, dequalinium chloride, polyhexamethylene biguanide, povidone iodine and hydrogen peroxide have been administered to women with BV as vaginal suppositories, bioadhesive gel formulations and occasionally loaded on pessaries. There are only sporadic reports of antimicrobial resistance against antiseptics agents, and they are safe for mucosal applications in appropriate concentrations and without systemic exposure [113]. Stray-Pedersen *et al.* have shown that vaginal douching with 0.2% chlorhexidine during labor can reduce both maternal and early neonatal infectious morbidity, but the main target of this treatment was to reduce the transmission of *Escherichia coli*, Group B streptococci and *Staphylococcus aureus* and to prevent early onset neonatal sepsis [114]. Dequalinium chloride showed *in vitro* and *in vivo* similar antibacterial and antifungal properties than povidone iodine [115,116] and its vaginal use was recently found to be as effective as clindamycin cream in a single-blind, randomized trial in women with BV, and a nonsignificant reduction of *Candida* infection was found in the dequalinium group [117]. Besides one study showing slightly better results in 15 days after treatment of acute BV than when only vaginal lactobacilli were applied [118], no studies show a benefit of povidone iodine. Nevertheless, the product is frequently used by women with BV and other abnormal conditions of the vagina, most likely because of the temporary relief of the symptoms because of the vaginal rinsing effect itself. Unknown allergy of iodium may cause severe allergic reactions in women.

Table 1. Overview of treatment modalities for bacterial vaginosis and the levels of evidence and activity of each therapy.

Product	Route	Dose	Grading of recommendation	Level of activity	Ref.
<i>Antibiotics</i>					
Metronidazole	<i>Per os</i>	500 mg 2dd × 5 days	A	++	[177]
	<i>Per os</i>	2 g stat, once	A	++	[93]
	Vag ovulae	500 mg 1dd × 5 days	A	++	[75,91]
	Vag ovulae	2 g once	B	++	[87]
	Vag cream	0.75% 1dd × 5 days	A	+	[77,80,92]
Tinidazole	<i>Per os</i>	1dd 1 g × 5 days	B	+	[85]
		2 g stat, once	B	++	[78,85-87]
	Vag tablets	1dd 500 mg × 14 days	B	+	[88]
Ornidazole	Vag tablets/sup	1dd 500 g × 7 days	C	+	[178]
	<i>Per os</i> + vag tablets	2dd	B	+	[89]
Secnidazole		500 mg × 5 days + 1dd 500 mg × 5 days			
	<i>Per os</i>	1dd 1 g to 2 g stat	B	++	[179]
	<i>Per os</i> + vag tablets orni	2 g stat, once + 1dd 500 mg × 5 days	B	+	[89]
Clindamycin	<i>Per os</i>	300 mg 2dd × 7 days	A	++	[180]
	Vag cream	2%	A	++	[81-84]
Rifaximin	Vag tablets	25 mg 1dd × 5 days	B	+	[110-112]
<i>Antiseptics</i>					
Chlorhexidine	Vag rinsing	1dd × Once	C	?	[114]
Dequalinium chloride	Vag tablets	1dd × 10 days	A	++	[115,116]
Povidone iodine	Vag rinsings	1dd × 7 days	D	?	
Nifuratel	Vag tablets	250 mg × 10 days	B	++	[121]
	Oral tablets	3dd 200 mg × 5days	B	++	[122]
<i>Acidification</i>					
Vitamin C	Vag tablet	250 mg 1dd × 6 days	A	+	[128-131]
Hydrogen peroxide	Vag rinsing	3% H ₂ O ₂ 1dd	B	-	[125]
Acetic acid	Vag gel	0.92% 2dd × 7 days	B	-	[124]
Lactic acid	Vag Suppo		B	-	[126]
Polycarbophil-Carbopol	Vag gel	1 dd × 35 days	B	+	[127]
<i>Probiotic</i>					
Lactic acid	Vag gel	1dd 2.5 mg × 7 days + 2 per week × 5 weeks	B	++	[134]
<i>Probiotic lactobacilli</i>					
<i>Lactobacillus reuteri RC14 and</i>	<i>Per os</i>	1dd × 28 days	B	+	[143]
<i>L. rhamnosus GR1</i>	Vag tablets	1dd × 5 days	B	+	[144]
<i>L. casei rhamnosus 35</i>	Vag tablets	1dd × 7 days	B	+	[135]
<i>L. brevis CD2, L. saliverus</i>	Vag tablets	1dd × 7 days	B	+	[131]
<i>FV2</i>					
<i>and L. gasseri MB335</i>					
<i>L. rhamnosus</i> (PB01-DSM 14870)	Vag tablets	1dd × 10 d × 3 months	B	- (acute) + (relapse prevention)	[138]
<i>and L. gasseri</i> (EB01-DSM 14869)					
<i>L. acidophilus</i> + 0.03 mg estriol	Vag tablets	1dd × 12 days	B	+	[133]

Grading of recommendation: A. High: further research is very unlikely to change our confidence in the estimate of effect, B. Good: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (only one high-quality study or several studies with some limitations), C. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate and D. any estimate of effect is very uncertain.

dd: Durante diam (per day); Vag: Vaginal application

In Eastern Europe, nifuratel vaginal tablets have increasingly been studied and used as a possible alternative treatment for BV. Its mode of action, originally designed for prevention and treatment of urinary tract infection, shows

excellent *in vitro* activity against *Gardnerella vaginalis*, *Mobiluncus* and *Atopobium vaginae*, whereas it is not active against lactobacilli [119,120]. Recently, two randomized controlled trials (RCTs) using vaginal nifuratel were presented

at the 8th European ESIDOG conference in London [121,122]. In one large, multicenter study totaling 727 women with BV, vaginal tablets of 250 mg nifuratel were compared with 100 mg metronidazole during 10 days, with slightly better therapeutic and clinical cure rates in the former [121]. In another study, 73 women with a treatment failure after 7 days of 1.5 g oral metronidazole were given either oral ($3 \times 200 \text{ mg} \times 5 \text{ days}$) or vaginal (500 mg + 200,000 IU nystatin $\times 8 \text{ days}$) tablets of nifuratel. All patients were asymptomatic after 28 days, and all 42 women with *A. vaginae* at baseline had complete eradication of this organism [122].

4.3 Acidifying agents

Acidifying the vagina with naturally occurring acids such as lactate or buffering the vagina against alkali exposure may enhance lactobacillary colonization and prevent anaerobic overgrowth [113,123]. Probably the impact of different acidic substances depends on the rate of absorption, metabolism, adhesiveness to vaginal mucosa and clearance by vaginal discharge [124]. Although it has been emphasized that in normal microflora more H_2O_2 producing lactobacilli are present than in BV, it is not wise to apply vaginal washings with 3% H_2O_2 solution, as it caused a higher failure rate than metronidazole and caused severe caustic side effects on the vaginal epithelium [125]. In another study, 0.92% acetic acid-based gel applied twice daily for 7 days was not superior to a placebo [124]. Also, lactic acid suppositories were less effective than metronidazole and equivalent to placebo in women with BV [126].

Polycarbophil–Carbopol-based vaginal gel during a 5-week treatment course, however, was found to be effective: after 6 and 12 weeks, respectively, 97 and 83% were cured according to the definitions of these authors versus 5 and 8% in the placebo group [127]. In this study, however, cure was defined as absence of abnormal vaginal discharge, low pH, negative odor and Nugent < 7, without considering presence or absence of clue cells or the typical anaerobic type bacterial flora, as seen in women with asymptomatic, yet often recalcitrant and/or recurrent, partial or full-blown BV [54].

Ascorbic acid is available as silicon-coated tablets containing 250 mg vitamin C that ensure long-lasting reduction in vaginal pH and does not produce irritation [128]. Bacteria such as lactobacilli, capable of reproduction even at low pH are favored in growth, but undesirable anaerobes are severely inhibited by vitamin C-induced vaginal acidification [129].

Peterson *et al.* [129,130] reported effective and safe use of vaginal vitamin C in a 6 days monotherapy regimen in the management of BV. Recently, its safety and pH-lowering capacity was confirmed in pregnant women's abnormal vaginal microflora: pH and microflora improved, both after an induction dose of daily treatment during a week, as after maintenance treatment with a three-times-a-week schedule [131].

4.4 Prebiotics

A prebiotic contains nutrients that support the growth of lactobacilli and aids in restoring the vaginal microflora in a most natural way, just supporting the growth of the endogenous lactobacilli. Witkin *et al.* have demonstrated that application of lactate to peripheral blood cells provokes an immune stimulation of IL-23 after lipopolysaccharide stimulation, which indicates that it could enhance resistance against *E. coli*-dominated microflora, such as in AV, but not BV [132]. When tested on vaginal mucosal cells, this group found an enhanced production of selective cytokines and increased natural antiviral defense system [133]. Coste *et al.* performed a randomized study of a prebiotic gel versus placebo in an adjuvant setting, showing that it resulted in a more complete normalization of the vaginal flora (Nugent score) and pH than placebo [134].

4.5 Probiotics

Probiotics are defined as live microorganisms which, when administered in an adequate amount, confer a health benefit to the host. Probiotics have been shown to displace and kill pathogens and modulate the immune response [135,136]. Various *in vitro* studies have shown that specific strains of lactobacilli inhibit the growth of bacteria causing BV by producing H_2O_2 , lactic acid, bacteriocins and inhibit the adherence of *G. vaginalis* to the vaginal epithelium [137].

In one *placebo-controlled* study, vaginal use of three probiotic lactobacilli (*Lactobacillus brevis*, *L. salivarius* and *L. gasseri*) gave better cure rates than placebo in symptomatic women with BV [138].

In *head-to-head comparison* studies comparing the efficacy of probiotic therapy with antibiotic therapy in women with acute BV, a 5-day regimen of vaginal lactobacilli GR-1/RC-14 showed equal results after 1 – 4 weeks than 75% metronidazole vaginal gel [139]. However, in this study the cure rates of metronidazole were only 55% after 6 days, which is, even with the strictest criteria, rather low. Further, 7 years later, still no single study has been able to repeat these findings, although the implications of confirmatory studies consolidating these data would be enormous. In another study, women with abnormal vaginal flora, also including women with other flora types than BV, were randomized to receive either 12 days of lactobacilli with 0.03 mg of estriol or 500 mg metronidazole vaginally for 6 days [140]. One week after treatment the failure results were equal, but after 4 weeks metronidazole was superior, indicating that in order to obtain long-term effects, repetitive application with lactobacilli may be indicated.

Adjuvant therapy after antibiotic therapy with metronidazole or clindamycin with *L. acidophilus* [141], *L. casei rhamnosus* (Lcr35) [142] or *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 (GR-1/RC-14) [143] after therapy was able to provide better cure rates of symptomatic BV and diminish the frequency of recurrences during 1 – 6 months follow up [144].

Larsson *et al.*, in a randomized, double-blind, placebo-controlled study using *L. rhamnosus* and *L. gasseri* followed after 2% clindamycin vaginal cream, could not show improvement of BV therapy during the first month, but adjunct treatment with lactobacilli significantly increased the time to relapse [145]. As other studies showed no improvement of vaginal probiotic use in women with BV, we need further RCTs with larger samples of symptomatic women, comparing lactobacilli with placebo and/or antibiotics [146].

5. Prevention of recurrences of BV

Women with frequent recurrences need extra attention to minimize the burden that BV imposes on their quality of life. In one placebo-controlled, randomized trial, weekly vaginal metronidazole was compared to placebo during 16 weeks, showing a significant difference in 70% of women being symptom-free in the treatment group as against only 30% in the placebo group [147]. However, even with metronidazole maintenance therapy, only 35% of patients and 20% of controls were still without recurrences, at 12 weeks post therapy. Further, patients having received vaginal metronidazole cream suffer from vulvovaginal candidosis more often than placebo users ($p = 0.02$).

In order to prevent taking antibiotics in repetitive courses, the adjuvant use of probiotics after an initial course of antibiotics has been tested in a number of RCTs. For the duration of 1 month after treatment with 1 g/day metronidazole for a week, 125 premenopausal Nigerian women with BV were treated with oral *L. rhamnosus GR-1* and *L. reuteri RC-14* or placebo, leading to 88% complete cure rates in the lactobacillus group (LB) versus 40% in the placebo group ($p < 0.001$) and none of the LB-treated women had BV vs 30% in the placebo group [144]. Also in placebo-controlled, randomized trials, vaginal application of probiotics following treatment of BV or other forms of vaginitis were efficient in reducing the post-treatment cure rate [141] or in preventing recurrences of BV over a 6 months period [145].

Recently, monthly vaginal application of vitamin C during 6 days after menses was able to reduce the BV recurrences for 32 to 16% of patients over 6 months [149].

6. Treatment of BV in pregnancy

Till a decade ago, treatment of BV during pregnancy caused concerns because of teratogenic risk of high doses of metronidazole in animals. Progressively, however, this risk has never been confirmed in humans treated with physiological doses of metronidazole or clindamycin, and hence they are no longer ill-advised, although in some countries their use during the first trimester is still ill-advised.

Most studies show a consistent increase in risk of pregnancy complications, such as failed implantations after embryo transfer, increased spontaneous miscarriages, preterm rupture of the membranes, chorioamnionitis, preterm delivery and

postpartum endometritis, in women with abnormal vaginal flora (AVF) or BV [34-51,148,150-152]. In follow up, the predominance of certain strains of lactobacilli, especially *L. crispatus*, seems to provide long-term protection against abnormal vaginal flora, more than the presence of *L. gasseri* and *L. iners* [153]. The latter even seems to be a destabilizing factor, increasing the risk of developing BV over time. Treatment studies of BV have been less consistent, leading to numerous meta-analyses, of which some claimed a reduced complication rate in subgroups of patients at high risk for preterm delivery [47,154], but most found no beneficial effect at all, especially in low-risk women [155-163]. In one careful, large RCT treating women with BV, metronidazole did not show any benefit in the prevention of preterm birth compared to placebo [164], while in two other RCTs the use of metronidazole was even disadvantageous, causing an increased rather than a decreased risk of preterm birth [165,166]. Further, in at least two meta-analyses, metronidazole was found to increase the risk of adverse pregnancy outcome [162,164]. On the other hand, although older RCT studies with vaginal clindamycin did not seem to influence the preterm birth rate [167-170], three

more recent RCTs using the broader spectrum antibiotic clindamycin provided beneficial evidence of reduced preterm birth rates, either given orally or vaginally [171-174]. Timing of medication – as early in pregnancy as possible or at least before 20 gestational weeks – seems to be important according to one study [171]; however, in the most recent meta-analysis, screening for and treatment of BV in pregnancy does not seem to lead to any reduction in preterm delivery [174]. Still, according to the same review and analysis, treatment did reduce early pregnancy losses before 20 weeks, and treatment of abnormal vaginal flora or intermediate flora (clindamycin) did reduce preterm birth by over 50%, indicating that in pregnancy other types of abnormal vaginal flora than BV, such as AV, probably play an important role.

Non-antibiotic therapy has also sporadically been tested for women with AVF or BV in pregnancy. In 1990, Holst and Brandburg reported a clear benefit of using acidifying cream for BV in a small group of women during pregnancy [175], but this paper was never followed by larger series. A Cochrane review of all randomized trial using probiotics indicated a clear reduction of vaginal infection after the use of oral or vaginal *L. acidophilus* containing milk products or yoghurt, but data on the outcome of pregnancy were lacking [176].

7. Expert opinion

The authors see three major challenges in BV treatment research. One is to develop drugs with better cure rates than the current gold standards, metronidazole and clindamycin, which neither achieve therapeutic cure rates > 65 to 70% after 1 month and which allow recurrence rates of 50% after 6 months. Part of this challenge may only be resolved by applying more stringent diagnostic techniques. Indeed, not

all women fitting the diagnosis of BV according to clinical (at least three of the four Amsel features) and/or laboratory (Nugent score > 7 on Gram-stained vaginal smears) display the same microbiological or metabolic characteristics of the disease. Metagenomic and proteomic analyses of the vaginal microflora have shown some types of BV to express *A. vaginae*, whereas others harbor *L. iners*, *Veillonella* sp., *G. vaginalis* or other bacteria as the main microorganism. As the sensitivity of these microorganisms to antibiotics is variable, neither clindamycin nor metronidazole, and probably no other, will be able to cover all with sufficient efficacy to accomplish complete cure. Hence, we might need to individualize the treatment according to the subtype of the abnormal/BV flora, in order to determine the most adequate therapy to obtain optimal results. Also, a more complete diagnosis of the at-times complex abnormal findings may be warranted, as a failure to detect a concomitant AV or *Trichomonas* infection may lead to a suboptimal treatment choice. Antibiotics may have to be adapted to the breakdown of the biofilm structure and/or to the proteomic and metabolomic features of certain subtypes of BV, in order to be effective and provide long-term cure and prevention of recurrences.

A second challenge is to adjust the therapy with the purpose of preventing recurrences. To achieve this goal, either the

replacement of classical antibiotherapy by alternative therapies, such as vitamin C, probiotic lactobacilli or antiseptics, or an adjuvant therapy to precede antibiotherapy may be the future management option of choice. Definitely more research is needed, not only to test for disappearance of the targeted microorganisms due to treatment but also to test the changes in specific biomarkers such as proteins, metabolic products and biofilm features.

A third challenge, only briefly addressed in this contribution, is the development of a treatment that not only decreases the signs and symptoms of BV, but rather its complications in pregnancy. Till date, the best treatment and timing to prevent BV-associated complications in pregnancy are not known, and several randomized, placebo-controlled studies, especially with metronidazole have given negative results. Although studies are scarce, the authors' best guess would be to combine repeated testing and retreatment with alternative (probiotic, acidification, etc.) maintenance therapy to prevent preterm labor and rupture of membranes.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers

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