S1-Guideline on Bacterial Vaginosis in Gynecology and Obstetrics

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S1-Leitlinie Bakterielle Vaginose in Gynäkologie und Geburtshilfe

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1 Introduction

Normal vaginal flora of sexually mature women consists of lactobacilli, transient or commensal anaerobic and aerobic bacteria, and Candida species from skin and gut flora. The normal pH value of vaginal flora is 3.8–4.4. Lactobacilli predominate in the vaginal flora, primarily L. crispatus, L. gasseri, L. iners and L. jensenii, depending on ethnicity. Normal pH values differ significantly between ethnicities, ranging from 3.8 to 5.2. Some healthy women have no lactobacilli in their vaginal flora; the percentage of women with lactobacilli differs depending on ethnicity; the percentage for Caucasian women is around 9%, for Hispanic and African women the percentage is more than 30% with normal pH values of around 5 [14,43]. At present, there are no studies into this issue for Europe.

Bacterial vaginosis (BV) is the most common microbiological disorder of the vaginal flora in sexually mature women. The prevalence of BV differs, depending on ethnicity; it is 2.4 times more common in women of African descent [13]. In Europe, the prevalence ranges from 5% in women who come for regular gynecological check-ups to more than 30% in women treated in clinics for sexually transmitted diseases. The reported prevalence in pregnant women is between 7 and 22% [3,9,15,22,25].

Psychosocial stress is a significant risk factor for BV [39]. There are also indications of gene–environment interactions as additional risk factors and of gene polymorphisms affecting genetic control of the individual's immune response to BV [35]. The abnormal oral conditions of periodontal disease have been found to be significantly correlated with disturbed vaginal flora in BV [46]. Vitamin D deficiency was identified as a risk factor for BV in pregnant women [13].

Microarray technology has been used to detect microorganisms associated with BV; in addition to Gardnerella (G.) vaginalis and Atopobium (A.) vaginae, bacteria of the genera Megasphaera, Dialister, Mobiluncus, Prevotella, Leptotrichia, Sneathia, Peptostreptococcus and others were identified [4,14]. There are several strains of G. vaginalis with different properties [6].

The most common cause of BV is probably sexual transmission [6,7,10,42,53]. Vitamin D deficiency is also being discussed as a risk factor for BV [13]. Typically, the numbers of H_2O_2-producing lactobacilli species are reduced in women with BV compared to women without BV [8].

Only around 50% of affected women present with characteristic symptoms such as increased homogeneous vaginal discharge or a fishy odor on alkalinization [26]. Many women with BV remain asymptomatic. Increased vaginal discharge can cause vulvar irritation.

2 Diagnosis

According to the diagnostic criteria proposed in some studies, BV is diagnosed when at least three of the following four findings are present at gynecological examination [1]:

- thin, homogeneous vaginal discharge
- vaginal pH greater than 4.5
- amine odor (particularly after alkalinization with 10% potassium hydroxide solution [KOH])
- > 20% clue cells on wet mount. (Gardner and Dukes [11] called the typical epithelial cells covered with bacteria found on vaginal wet mount "clue cells" because they offered a clue to the diagnosis of BV).

Alternatively, BV can be diagnosed by Gram-staining vaginal fluid (Nugent score) [40].

Typical findings for BV are decreased concentrations of certain facultative anaerobic Lactobacillus strains and 1000-fold higher concentrations of anaerobic microorganisms. G. vaginalis is also present at 100-fold higher concentrations. Thus,

bacterial vaginosis is characterized by a microbial imbalance, with a marked shift towards increased concentrations of anaerobic microorganisms (see above) to the detriment of facultative anaerobic flora, particularly Lactobacillus species [4,8,16,21,30,36]. Particularly L. iners, which is present in normal vaginal microflora, was found to have a tendency to replace L. crispatus or L. gasseri, with higher concentrations of L. iners found in the vaginal fluid of women with BV [58,63].

3 Bacterial Biofilm

A prominent feature of BV is a polymicrobial biofilm adherent to the vaginal epithelium. The biofilm consists mainly of G. vaginalis and A. vaginae, but lactobacilli are also present in lower concentrations [50]. Bacterial biofilms are typical for chronic and/or foreign body-associated infections. Guideline-directed treatment does not eliminate the biofilm in women with BV [51]. The biofilm has also been detected in epithelial cells in the urine of women with BV and of their sexual partners [53] and in individual samples of washed donor semen from sperm banks [54] but not in the (peri-)anal area of women with BV [52]. The biofilm has also been found on endometrial samples obtained during curettage and on fallopian tube epithelia of women with BV [55].
Since 1978, standard recommended therapy consists of oral metronidazole [42], but metronidazole does not reliably eliminate the biofilm, even when clinical impression, pH and wet mount appear to show a cure [51] (see also Recommendations for Treatment below).

4 Bacterial Vaginosis and Gynecology

Women with BV have a higher risk of infection ascending from the cervix to the endometrium (endometritis) to the adnexa (salpingitis, tubo-ovarian abscess) [17,28,55]. The risk also appears to be increased in women with an intrauterine device in situ [2,9,11]. Endometritis resulting from BV can lead to abnormal bleeding [32]. Women with BV also have a greater predisposition to urinary tract infection [11,26,28]. Infectious morbidity after hysterectomy is also increased [12,20,31,48,49,60].
There are some indications that BV represents a risk factor for ascending infection after termination of pregnancy and for spontaneous abortion [21,29,55].

5 Bacterial Vaginosis and Obstetrics

Pregnant women with BV have a higher risk of premature rupture of membranes, preterm labor and preterm birth due to ascending infection. Fever during and after delivery is also more common (post-partum endometritis and wound infection). These infections have been found to be histologically correlated with chorioamnionitis and with positive microbiological cultures from amniotic membranes and placenta. Women after cesarean section are particularly at risk [5,12,15,17–19,33,34,37,47,55,56,59].
Numerous studies have investigated the treatment of BV during pregnancy [27,33,34,41]. Treatment consists of the systemic administration of either metronidazole or vaginal clindamycin cream. Some studies have indicated that systemic antibiotic treatment of BV after the 1st trimester of pregnancy can reduce the number of preterm births in high risk groups (e.g. previous history of preterm birth). Intravaginal application appears to be less suitable to reduce the risk of preterm births in high risk groups.
Studies in Thuringia and Vienna have shown that screening for BV even in pregnant women without a history of preterm birth followed by treatment (oral or intravaginal application) is effective; these findings are supported by the meta-analysis of Varma and Gupta [22,23,25,56].
In the Erfurt trial for the prevention of preterm births, pregnant women regularly measured their vaginal pH themselves. The active participation of pregnant women meant that this strategy detected changes in pH levels very early on, allowing a number of risk factors relevant for late spontaneous abortion and preterm birth to be treated quickly. Statistical analysis of the trial data confirmed the positive impact and represented a breakthrough with regard to the availability of a feasible and universally applicable measure to prevent preterm birth [45].
Preventing preterm births with the help of screening to detect and treat genital infections, particularly BV, is one strategy to optimize and rationalize healthcare. The cost-benefit analyses of this approach carried out by various parties have been controversially discussed and their methodology has been criticized [45]. Regular determination of vaginal pH has been found to be widely accepted by pregnant women, making the method highly feasible [22,23].

6 Recommendations for Diagnosis

The criteria listed above should be used to exclude BV in all women prior to placing an intrauterine device and prior to any intrauterine intervention. Women should receive comprehensive antibiotic treatment either prior to intervention or perioperatively. A predisposition to BV should be considered in patients with bleeding disorders or recurrent urinary tract infections.
Determination of vaginal pH and wet mount of vaginal flora are suggested for screening prior to a planned pregnancy or early on in pregnancy. These diagnostic measures can be used to exclude genital infections with a high level of confidence and with little expenditure of time. This applies particularly to women with a history of preterm birth. Antibiotic treatment is indicated if BV is diagnosed. Pregnant women with a history of preterm birth and a diagnosis of BV should receive systemic treatment with antibiotics. Wet mount evaluation should be done prior to terminating a pregnancy.

7 Recommendations for Treatment

Metronidazole and 2% clindamycin vaginal cream are two highly effective anaerobicides used to treat bacterial vaginosis. Non-pregnant women can be treated with oral metronidazole administered 2 × 500 mg/day for 7 days. Both a single dose administration of oral metronidazole and 2 × 2 g metronidazole administered at an interval of 48 hours have acceptable cure rates. Good results were also reported for intravaginal metronidazole applications consisting of 1–2 × 500 mg metronidazole vaginal tablets daily for 7 days. The daily application of 5 g of 2% clindamycin vaginal cream for 7 days is another effective alternative to treat BV. Placebo-controlled studies have reported similar cure rates for 1 × 2 g oral metronidazole and 2 × 1 g metronidazole applied

intravaginally on 2 consecutive days (89.9% vs. 92.5%), although compliance was significantly higher for vaginal applications [24]. Individual studies have reported recurrence rates after treatment with 10 mg dequalinium chloride vaginal tablets for 6 days [61] or 1 × 250 mg nifuratel vaginal tablets for 10 days [38] similar to the recurrence rates for standard metronidazole treatment.

7.1 Treatment of the bacterial biofilm

None of the recommended treatments eliminate the adherent bacterial biofilm [51]. There is currently no evidence-based treatment available that minimizes the risk of chronic manifestation and recurrence. The bacterial biofilm and its presence in the upper genital tract of women and in partners of women with BV appears to be the explanation for the fact that the cure rate after 3 months is only 60–70% and is even lower after 6 months [30, 57].

New findings from studies of probiotic Lactobacillus strains and clinical studies examining ways of lowering the recurrence rates of BV after standard treatment using probiotics or acidic applications to reduce vaginal pH have shown that these methods can be effective and found that they reduced the rate of BV recurrence by around half [24, 44, 62].

7.2 Treatment during pregnancy

Despite theoretical concerns and after consultation with the patient, metronidazole can be administered systemically as described above after the 1st trimester of pregnancy to treat pregnant women with BV. Alternatively, treatment can also consist of local vaginal application of 500–1000 mg metronidazole for 7 days. Oral clindamycin 2 × 300 mg/day for 7 days can be prescribed after the 1st trimester of pregnancy. Daily intravaginal application of 5 g of 2% clindamycin vaginal cream for 7 days has similar cure rates as metronidazole; the reported side-effects are minimal and there are no concerns about its application during pregnancy. However, studies have shown that treatment of BV during pregnancy as a prophylactic measure against preterm birth in high risk patients (e.g. previous history of preterm birth) is only effective if treatment is systemic [34].

7.3 Co-treatment of the partner

Although the typical bacterial biofilm found with BV has also been found in cells from the urine or sperm of male partners of women with BV, there is currently no scientific basis for routine co-treatment of partners, and it is therefore currently not recommended.

Consensus Process

These recommendations were compiled by the following members of the *Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie* (Professional Society for Infections and Infection Immunology [AGII]) of the *Deutsche Gesellschaft für Gynäkologie und Geburtshilfe* (German Society for Gynecology and Obstetrics [DGGG e.V.]):

- Prof. Dr. med. Werner Mendling, Wuppertal (overall responsibility)
- Prof. Dr. med. Joachim Martius, Agatharied
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The present version was approved by all of the authors in July 2013.

The revision was confirmed in August 2013 by the Board of the *Deutsche Gesellschaft für Gynäkologie und Geburtshilfe* (German Society for Gynecology and Obstetrics).

The Guideline will remain valid until 08/2016.

Conflict of Interest

Prof. Mendling received royalties for scientific consultancy or lectures by Abbott GmbH & Co. KG Wiesbaden/Germany, Medinova AG Zürich/Switzerland, Pierre Fabre GmbH Freiburg/Germany, Dr. August Wolff GmbH & Co. KG Bielefeld/Germany and Polichem S.A. Lugano/Switzerland. Prof. Martius declares no conflict of interest. Prof. Hoyme received royalties by Dr. August Wolff GmbH & Co. KG Bielefeld.

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