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Original Contribution

CONCEPTS ON ASYMPTOMATIC BACTERIAL VAGINOSIS

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ABSTRACT

Bacterial vaginosis is a state of imbalance of the vaginal microbiota with prevalence of anaerobes and a relative lactobacilli deficit. The main pathogens are *Gardnerella vaginalis* species of heterogeneous phenotypic characteristics and virulence, forming a bacterial polymicrobial biofilm on vaginal epithelial cells.

A symptomatic infection clinically manifested by a homogeneous grey-white vaginal discharge with a fishy smell by all means requires a treatment regimen.

The concepts on asymptomatic bacterial vaginosis have not reached a definite consensus regarding the fact whether treatment is required – the interpretation of its sexual transmission is ambivalent and it is unclear whether there are any differences in the pathogenesis and levels of complications between the two clinical manifestations of bacterial vaginosis.

An early therapeutic approach is available for asymptomatic pregnant women; however, it does not demonstrate a significant difference in the incidence of obstetric complications.

Fluctuations and transitoriness in vaginal microbiota composition, manifested by spontaneous transition to verified lack of infection destabilizes the view point that treatment is mandatory in asymptomatic non-pregnant women. Recommendations are available concerning preoperative regimens, prevention of gynaecological and obstetric complications aiming at prevention of sexual transmission and infection with other sexually transmitted diseases.

The treatment approaches to verified bacterial vaginosis involving combined standard and alternative regimens have shown unsatisfactory long-term results, and the evidence so far is insufficient to absolutely confirm or refute the usefulness of treating an asymptomatic infection.

Key words: bacterial vaginosis, bacterial biofilm, asymptomatic, metronidazole, antibiotic resistance

INTRODUCTION

The distribution of bacterial vaginosis (BV) is 23-29 % worldwide, 5-30% in Europe, 29.2% in USA, 7-22% involving pregnant women, and 84% asymptomatic.

Giving the names 'non-specific vaginitis', '*G.vaginalis* vaginitis', '*Haemophilus vaginalis* vaginitis' are all attempts to define the etiologic agent in BV. A study has reported 20 heterogeneous *G. vaginalis* morphotypes, 10 of which were genome sequenced for analysing general and unique pathogenic genes, biofilm formation and antibiotic resistance.

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Gardnerella leopoldii, *G. piotii* and *G. swidsinskii* were re-classified based on phenotypic characteristics. Adhesion, secretion, Fe and Mg absorption, immune escape and toxins are considered virulence factors in dominant strains. *Gardnerella spp*. have shown a stronger adhesion to vaginal epithelium, as well as stronger tendency to biofilm formation. This may have helped the adhesion of other anaerobes and is in correlation with BV manifestation and recurrence. *Gardnerella* spp. in the absence of virulence factors are associated with vertebral osteomyelitis, retinal vasculitis, acute arthritis of the hip joint and bacteraemia. The study has reported strain resistance to certain lincosamides, macrolides, aminoglycosides, tetracycline, with 7 out of 10 resistant to metronidazole. Clindamycin and

metronidazole have not been effective for all prevalent strains; development of a progressively thicker biofilm is likely to be an evolutional tendency. The polymicrobial biofilm has contained also *Atopobium vaginae*, bacteria from the genera *Prevotella, Megasphaera, Dialister, Mobiluncus, Leptotrichia, Sneathia, Peptostreptococcus*, etc. (1-3).

Predisposition to BV occurs in women with vitamin D deficit, black women, patients with coagulation disturbances or recurrent urinary infections, those who smoke or use vaginal douche (2, 4).

Proofs that BV can be sexually transmitted are based on similarity in the genital microbiota of the partners – African-American women in sexual relations with women, heterosexual monogamous couples; 95-100% *G. vaginalis* has been isolated in heterosexual partners. Presence of *G. vaginalis* does not always result in BV. It has been isolated in virgin women as well. It is very likely that the virulent *G. vaginalis*, *Prevotella bivia* and *Atopobium vaginae* are associated with symptomatic infection and the non-pathogenic ones are associated with an asymptomatic state; however, the range of non-virulent species in the polymicrobial biofilm is not known (2, 3, 5, 6).

DISCUSSION

Prevalence of lactobacilli is an essential characteristics of the vagina of healthy women, with pH varying from 3.8 to 5.2. There is absence of lactobacilli in some and marginal presence of fungi in others (2, 7).

BV diagnosis is verified by PCR tests, 3 out of 4 Amsel criteria – homogeneous grey-white vaginal discharge, pH >4,5, amine odour after adding a drop of 10% KOH to the discharge, clue cells >20%, and by Nugent criteria, a score ≥7 out of10 – quantitative detection of bacterial morphotypes and lactobacilli in the vaginal smear (2, 8).

A study on both symptomatic BV (sBV) with marked exfoliation of superficial mature epithelial cervico-vaginal cells and asymptomatic BV (aBV) involving mild exfoliation, has admitted that the above-mentioned pathologies may be temporally separated phases of one and the same state and not two distinguishable types of BV (9).

A polymicrobial *G. vaginalis* biofilm has been detected in the endometrium and the fallopian tubes, which accounts for the complications. Bacterial vaginosis is associated with an increased risk of sexually transmitted infections - HIV, chlamydia, gonorrhea, trichomoniasis, *Mycoplasma genitalium*, HPV, HSV-2. BV has been found to be in correlation with the following: miscarriage in the first trimester in IVF, late abortion, chorioamnionitis, premature delivery, low birth weight, postpartum and post-abortion endometritis, pelvic inflammatory disease, tubal factor infertility, recurrent or persistent BV, persistent HPV infection. There is an increased risk of postoperative surgical infections following obstetric or gynaecological surgery, whereas metronidazole treatment considerably reduces vaginal cuff infection following hysterectomy (3, 10-14)

Concepts and algorithms of BV management, pursuant to the WHO directives and recommendations, as well as those of the Centres of Disease Control and Prevention, include induction, suppressive and combined therapy. Verified symptomatic BV in non-pregnant women is treated either with Metronidazole 2 x 500 mg perorally for 7 days, or Metronidazole vaginal gel 0,75%, 5g, one applicator intravaginally per day for 5 days. Effectiveness in the range 70-80% has been reported, whereas the 7-day oral regimen of separate doses has achieved over 90% early cure and up to 80% after 4 weeks of treatment. It has not been clarified whether the single dose of 1.3% intravaginal Metronidazole is more effective than the preferred dose of 0.75% Metronidazole application for many days (11).

Oral Metronidazole 1x2 g has been found effective in 89.9%, whereas 2x1 g Metronidazole applied for 2 consecutive days has been found effective in 92.5%. Intravaginal Metronidazole in a dosage of 2 g has a considerably lower efficacy - 46% on the 21-st day and 86% in the 7-day regimen. Other regimen plans include 2x2 g of Metronidazole, 48 hours apart; Metronidazole vaginal tablets 1-2x500 mg for 7 days (2, 15).

The 14-day Metronidazole treatment has achieved better early effect, but in the long run the results have proved to be similar. Clindamycin cream 2%, 5g, has also been applied as a single intravaginal applicator daily for 7 days as preferable to the oral administration; one-dose and multi-dose

regimen plans have shown similar results, with alternative regimens Clindamycin 2x300 mg daily for 7 days and Clindamycin vaginal ovules 100 mg applied for 3 days (11).

The treatment regimen of Tinidazole, half-life 12-14 h, oral dose of 1g once a day for 5 days has been found more effective than 2 g oral Tinidazole once a day for 2 days. It is as effective as, but not better than Metronidazole, whose half-life is 7-8 h. A single dose is as effective as the vaginal Clindamycin cream. Secnidazole (half-life 17-19 h) has been applied in single doses of 1g, 2g oral granules as an alternative recommendation. Dequalinium chloride vaginal tablets, a topical antiseptic, at a dosage of 10 mg once daily for 6 days have been effective in 81.5%, as compared to Clindamycin cream being effective in 78.4 %, achieving early cure up to the 14-th day. The incidence of recurrence following Dequalinium chloride treatment for 6 days or Nifuratel treatment regimen of 1 x 250 mg for 10 days has been found similar to the recurrence in standard Metronidazole treatment (2, 11).

Probiotic *Lactobacillus* strains and acidic applicators following standard treatment reduced recurrence cases by ½ through lowering pH, but another study found that proof of probiotic efficacy is insufficient, as well as regarding the optimal route of administration – oral or vaginal, time of administration with regards to the antibiotic treatment, independently or as an adjunct, dosage and duration of administration. *Lactobacillus crispatus* seems to be promising. Boric acid as vaginal suppositories has been applied to treat recurrent BV in addition to suppressive antimicrobial regimen (2, 3, 11).

Erythomycin, tetracycline, ampicillin, amoxicillin are not recommended because of ineffectiveness, as well as lactic acid, acetic acid and ascorbic acid gels, azithromycin, chlorhexidine, hydrogen peroxide, isolated vaginal boric acid, povidone-iodine vaginal douches. Long-term suppressive oral or topical Clindamycin regimens are not recommended in recurrent BV due to toxicity, ineffectiveness and yeast co-infection, as compared to Metronidazole gel regimen (11).

Pregnant women with symptomatic BV are treated for symptomatic relief with oral regimens considered more effective in the prevention of obstetric complications – either Metronidazole 2 x 500 mg or 3 x 250 mg for 7 days, or Clindamycin 2 x 300 mg, for 7 days. Topical applications are as effective as the oral ones – Metronidazole gel 0.75% for 5 days or Clindamycin cream 2%, 5 g for 7 days. An increased teratogenic risk has not been reported in Metronidazole exposure in the first trimester; nevertheless, WHO recommends using it with greater care. It has been found to be mutagenic in bacteria, carcinogenic in mice, although no harm has been proved in people. Tinidazole is not recommended. It has not been ascertained whether vitamin D supplementation reduces BV prevalence in pregnant women (4, 11).

In symptomatic breastfeeding women oral regimens are preferred to intravaginal ones. Metronidazole 2 x 500 mg for 7 days is preferred to Clindamycin 2 x 300 mg for 7 days, because of Clindamycin - associated gastrointestinal symptoms in breast-fed children. About 30% of the intravaginal Clindamycin is absorbed, although in this way the adverse reactions of the oral drug are avoided; the plasma levels of Metronidazole gel 0.75% are by 2% lower than those of the oral 500 mg Metronidazole. Ingestion of a single dose of 2 g Metronidazole by the mother is too high for a breast-fed baby; therefore, breastfeeding is recommended to be 12-24 h after the last dose; in the case of Tinidazole it should be after 72 h (11).

Asymptomatic non-pregnant women who do not undergo gynaecological interventions are followed without treatment due to spontaneous passing to lack of infection in the course of a few months, self-restriction in 1/3 of the non-pregnant and ½ of the pregnant women; however, symptomatic vaginal candidiasis is possible after antibacterial therapy (11).

Patients with forthcoming or planned obstetric or gynaecological operations involving the vagina are treated irrespective of the symptoms for the purposes of prevention of postoperative complication in 10-75%. Ruling out BV is recommended prior to insertion of an intrauterine system (11).

Asymptomatic BV (aBV) – a positive laboratory result in the absence of an unusual vaginal discharge with fishy odour - poses treatment dilemmas. A longitudinal study has reported 78% asymptomatic cases, concluding that treating asymptomatic cases with a positive laboratory result is not justified. A study has

reported that without using Metronidazole gel 18.5% asymptomatic non-pregnant women develop symptoms on day 28, and another study has found that without treatment 12-18% and 44% asymptomatic cases develop symptoms after a month and in the 4th month, respectively (3).

Significant reduction of chlamydia-caused infections has been reported in treating BV-asymptomatic non-pregnant women with Metronidazole gel for 5 days, with subsequent use twice a week for 6 months. The treatment regimen most likely modifies the indole-rich environment, favourable for BV-associated bacteria, into a poor, tryptophan-depleted one, reducing chlamydia capability to survive (3).

Two meta-analyses have observed BV occurrence in women with tubal sterility (19% and 16%, respectively) with a considerably increased risk of preclinical loss of pregnancy. The first meta-analysis did not find increased risk of miscarriage in the first trimester; the second one found a connection with early miscarriage, although not significantly influencing live births. The conclusions suggest that BV may have bearing on the outcome of pregnancy and support aBV treatment in infertile women undergoing IVF (3).

Asymptomatic pregnant women at high risk with a history of premature delivery, may benefit from treatment, although no reduction in premature birth incidence has been found against the background of the BV-associated risks for pregnancy. No treatment criteria have been defined, screening and treatment are contradictory and have not been implemented. Asymptomatic breastfeeding women are not treated. Treatment regimens in pregnant women with aBV are restricted to Metronidazole and Clindamycin, other medications have not been accurately studied; the data available in publications reveal that only systemic BV treatment in pregnant women at high risk is an effective prophylaxis against premature delivery. The early, timely and proper treatment of women with aBV, non-infected with HIV and living in an environment with extensive HIV spread, is a preventive measure against getting infected during pregnancy, with subsequent unfavourable consequences for the pregnancy – the study involved 47% asymptomatic women (2, 3, 11, 16).

G. vaginalis infection has been associated with 25% premature rupture of membranes (PROM); 31.67% premature delivery (PD); according to others the risk is higher when BV has been diagnosed in early pregnancy; 32% endometritis has been reported – a percentage significantly exceeding the one observed in women with normal pregnancy (1).

A study has proved that treatment eradicates BV in pregnant women and there is evidence that when applied before 20 g.w. it reduces the risk of PD < 37 g.w. The application of treatment does not result in a reliable change in PD risk < 37 g.w., as well as in PROM in low-risk women. Treatment does not alter the risk of a subsequent PD in women with a previous one, although it may reduce the risk of PROM and low birth weight. Reduction of PD risk < 37 g.w. has not been observed in Clindamycin treatment (17, 14).

A study carried out in the USA has not found screening and treatment to be beneficial in pregnant women with aBV at low or medium risk of delivery before 32, 34, 37 g.w., PROM or low birth weight. The results in high-risk pregnant women were heterogeneous (18).

In Norway, low-risk pregnant women with aBV are not treated, although being about 50%. Clindamycin is associated with an unclear risk < 33 g.w., as well as a mild or no change in PD risk before 37 g.w., low birth weight or postpartum uterine infections, when applied for aBV in the second trimester and before 20 g.w. (19).

A meta-analysis (2011) of Clindamycin treatment of pregnant women with aBV < 22 g.w. has shown reduction of PD < 37 g.w., 3.7% *vs* 6.2%. The analysis in women at low or high PD risk revealed that the oral, not the vaginal Clindamycin regimen, reduces PD significantly. Another meta-analysis (2013) involving asymptomatic and symptomatic pregnant women revealed that the treatment eradicated BV, but even applied before 20 g.w. , as well as in high-risk women, it did not reduce significantly premature delivery before 37 g.w. A meta-analysis (2015) reported PD reduction after antibiotic treatment in the 2nd - 3rd trimester in high-risk pregnant women with BV, but not in women with history of premature delivery, without BV (11).

No screening for BV has been recommended in low-risk pregnant women, although some reports have suggested that aBV treatment in pregnant women affects premature delivery; however, no difference in PD incidence has been observed. The observations in asymptomatic high-risk pregnant women are contradictory and evidence for assessing benefits and harm from the screening is insufficient (3, 14, 20).

There is not sufficient evidence for recommending and establishing antibiotic treatment in asymptomatic sexual partners of women with confirmed BV, due to the lack of clinical and symptomatic improvement or reduction in the incidence of recurrence (2, 11).

Recurrent BV is defined as 3 or more infections per year. Possible mechanisms for the high level of recurrence - 30% in the 3rd month, 50% in the 6th -12th month,- are inadequate initial treatment or overall treatment improper for the bacterial community, impossibility to restore the normal vaginal microbiota dominated by lactobacilli, imprecise understanding of the pathogenesis of the recurrent or incidental BV. To prevent recurrence of infection, asymptomatic women with BV continue the suppressive treatment involving Metronidazole gel twice a week. Symptomatic persons are re-treated with a medication not previously used or with one that has produced best effect. For those who develop symptoms in the course of the suppressive treatment, vaginal boric acid is added at a dosage 600 mg once a day for 20 to 30 days, in combination with antibiotic treatment. After the last boric acid suppository one to two days of observation follow and at remission Metronidazole gel twice a week is started, for 4-6 months as suppressive treatment. Chronic suppressive treatment reduces recurrence. Persons sensitized to Metronidazole are desensitized or treated with topical Clindamycin cream. However, Clindamycin is associated with vaginal mycotic coinfections as adverse effect, in contrast to Metronidazole gel (11, 21).

A study found that persistent bacterial vaginosis was associated with *Clostridiales* and *Peptoniphilus lacrimalis*, assuming that the predictive value of the etiological range is significant in determining the risk resulting from treatment failure (22).

Another study offered a joint, both oral and topical treatment for the male partner, assuming that the skin colonization, which is immediately affected by the treatment, although not so markedly on day 28, is likely to participate in the pathogenesis of infection – BV occurrence and recurrence in men. It has been suggested that BV can be found in the prostate gland or can persist in male distal urethra after treatment, proliferating without treatment; the loss of effect from treatment on day 28 does not always result in a second BV occurrence in the vaginal microbiota of the sexual partners of men, which suggests that BV sexual transmission is not easy to interpret (3).

No treatment regimen has been approved for the prevention of chronic manifestation and recurrence or the eradication of the bacterial biofilm – its detection in the upper genital tract of the partners accounts for 60-70 % therapeutic effect in the 3rd month and a lower one in the 6th month. Transplantation of vaginal microbiota is a new, provocative treatment for women with BV, which at present is in its investigation stage. Some reports have stated that BV is a reversible infection due to spontaneous passing into a state without BV following menstruation, with no application of treatment (2, 3).

CONCLUSION

Treatment approaches to bacterial vaginosis, involving imidazole derivatives, lincosamides, and probiotics in induction, suppressive and combined treatment options, are not sufficiently effective in eradicating the polymicrobial biofilm; thus, high levels of chronic and recurrent infection are reported.

The concept of an early treatment approach in an asymptomatic infection, which involves a limited range of medications, treatment plans and exposure, is supported for pregnant women, although it does not reduce the incidence of premature deliveries. Screening is not implemented but pregnant women are assessed whether they are at high risk.

There is a risk of symptomatic vaginal mycosis if treatment is applied in non-pregnant women with asymptomatic bacterial vaginosis. Among others approaches, antibiotic-free treatment finds its place in asymptomatic non-pregnant women, due to the spontaneous restoration of the balance of vaginal microbiota.

Asymptomatic BV is not identified with a negative result for *Gardnerella vaginalis*

species. Asymptomatic BV is likely to be associated with non-pathogenic species, whereas the symptomatic infection is associated with virulent ones. Their heterogeneous genome structure demonstrates evolutionarily and progressively a thicker biofilm of varying degree of antibiotic resistance to the treatment regimens applied, a likely cause of the unstable therapeutic effect on the genital microbiota. Conceptual models of the etiology and pathogenesis of asymptomatic bacterial vaginosis and the differentiation of the virulent strains will present a definitive statement regarding the necessity of treatment.

REFERENCES

1. Zhang, K., Lu, M. et al. Antibiotic resistance and pathogenicity assessment of various *Gardnerella* sp. strains in local China, *Front Microbiol*. 2022 Sep 26:13:1009798.doi: 10.3389/fmicb.2022.1009798. eCollection 2022; www.frontiersin.org
2. Mendling, W. Martius, J., Hoyme, U B. et al. S1-Guideline on Bacterial Vaginosis in Gynecology and Obstetrics: Long version - AWMF Guideline, r egistration no. 015/028, July 2013 Langfassung - AWMF-Register Nr. 015/028, Juli 2013; *Geburtshilfe Frauenheilkd*. 2014 Jan;74(1):51-54. doi: 10.1055/s-0033-1360230; www.ncbi.nlm.nih.gov
3. Muzny, C., Schwebke, J. Asymptomatic Bacterial Vaginosis: To Treat or Not to Treat?, *Curr Infect Dis Rep*. 2020 Dec; 22(12): 32. Published online 2020 Nov 13. doi: 10.1007/s11908-020-00740-z; National Library of Medicine; www.ncbi.nlm.nih.go
4. Ma, L., Z., Zhang, Z. et al. Vitamin D deficiency increases the risk of bacterial vaginosis during pregnancy: Evidence from a meta-analysis based on observational studies, *Front Nutr*. 2022; 9: 1016592. Published online 2022 Nov 22. doi: 10.3389/fnut.2022.1016592; www.frontiersin.org
5. Zozaya, M., Ferris, M. et al. Bacterial communities in penile skin, male urethra, and vaginas of heterosexual couples with and without bacterial vaginosis. *Microbiome*. 2016; 4: 16. Published online 2016 Apr 19. doi: 10.1186/s40168-016-0161-6 www.pubmed.ncbi.nlm.nih.gov
6. Muzny, C., Lensing, S.et al. Incubation period and risk factors support sexual transmission of bacterial vaginosis in women who have sex with women. Sex Transm Infect. Author manuscript; available in PMC 2020 Jun 2.*Published in final edited form as:*Sex Transm Infect. 2019 Nov; 95(7): 511–515. Published online 2019 Mar 14. doi: 10.1136/sextrans-2018-053824; www.ncbi.nlm.nih.gov
7. Chee, W., Chew, S. Than , L. Vaginal microbiota and the potential of Lactobacillus derivatives in maintaining vaginal health, *Microbial Cell Factories* volume 19, Article number: 203 (2020); www.microbialcellfactories.biomedcentral.com
8. Hilbert, D., Smith, W. et al. Development and Validation of a Highly Accurate Quantitative Real-Time PCR Assay for Diagnosis of Bacterial Vaginosis. *J Clin Microbiol*. 2016 Apr; 54(4): 1017–1024.Published online 2016 Mar 25. Prepublished online 2016 Jan 27. doi: 10.1128/JCM.03104-15; www.pubmed.ncbi.nlm.nih.gov
9. O'Hanlon, E., D. Gajer, Pm et al. Asymptomatic Bacterial Vaginosis Is Associated With Depletion of Mature Superficial Cells Shed From the Vaginal Epithelium. *Front Cell Infect Microbiol*. 2020 Mar 10:10:106. doi: 10.3389/fcimb.2020.00106. eCollection 2020; www.pubmed.ncbi.nlm.nih.gov
10. Swidsinski, A., Verstraelen, H. et al. Presence of a polymicrobial endometrial biofilm in patients with bacterial vaginosis. *PLoS One*. 2013;8(1):e53997. doi: 10.1371/journal.pone.0053997. Epub 2013 Jan 8.; www.pubmed.ncbi.nlm.nih.gov
11. Sobel, J. Bacterial vaginosis: Initial treatment, 2023; Literature review current through: Jan 2024.This topic last updated: Sep 12, 2023; www.medilib.ir
12. Soper, D., Bacterial vaginosis and surgical site infections. Am J Obstet Gynecol. 2020 Mar;222(3):219-223. doi: 10.1016/j.ajog.2019.09.002. Epub 2019 Sep *Am J Obstet Gynecol*, 2020; pubmed.ncbi.nlm.nih.gov
13. Larsson, PG., Carlsson, B. Does pre- and postoperative metronidazole treatment lower vaginal cuff infection rate after abdominal hysterectomy among women with bacterial vaginosis? Infect Dis Obstet Gynecol. *Infect Dis Obstet Gynecol*. 2002;10(3):133-40. doi: 10.1155/S1064744902000133.; www.pubmed.ncbi.nlm.nih.gov

14. Asymptomatic bacterial vaginosis, 2019; www.health.gov.au; app.magicapp.org/?language=pl#/guideline/jm83RE
15. Swedberg et al. Comparison of single-dose vs one-week course of metronidazole for symptomatic bacterial vaginosis, *JAMA*. 1985 Aug;254(8):1046-9; www.pubmed.ncbi.nlm.nih.gov
16. Joyisa, N., Moodley, D. et al. Asymptomatic Bacterial Vaginosis in Pregnancy and Missed Opportunities for Treatment: A Cross-Sectional Observational Study, *Infect Dis Obstet Gynecol*. 2019 May 2:2019:7808179.doi: 10.1155/2019/7808179. eCollection 2019. 2019; www.pubmed.ncbi.nlm.nih.gov
17. McDonald, HM. Brocklehurst, P. Gordon,A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev*. 2007; (1): CD000262. Published online 2007 Jan 24. doi: 10.1002/14651858.CD000262.pub3; www.ncbi.nlm.nih.gov
18. Nygren, P.,Fu, R. Freemanet, M. al. Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: an update review for the U.S. Preventive Services Task Force, Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews 2008; www.ncbi.nlm.nih.gov
19. Myrhaug, H., Brurberg, K. et al. Treatment of Pregnant Women with Asymptomatic Bacterial Vaginosis with Clindamycin, Report from Norwegian Knowledge Centre for the Health Services (NOKC) No. 11-2010; 2010; www.ncbi.nlm.nih.gov
20. Owens, D., Davidson, K. et al. Screening for Bacterial Vaginosis in Pregnant Persons to Prevent Preterm Delivery: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020 Apr 7;323(13):1286-1292. doi: 10.1001/jama.2020.2684. www.pubmed.ncbi.nlm.nih.gov
21. Bradshaw, C., Sobel, J., Current Treatment of Bacterial Vaginosis-Limitations and Need for Innovation. *J Infect Dis*. 2016 Aug 15; 214(Suppl 1): S14–S20.Published online 2016 Jul 19. doi: 10.1093/infdis/jiw159; www.ncbi.nlm.nih.gov
22. Marrazzo, J. M. ,Thomas K.K.et al. Relationship of specific vaginal bacteria and bacterial vaginosis treatment failure in women who have sex with women, *Ann Intern Med.* 2008 Jul 1; 149(1): 20–28.doi: 10.7326/0003-4819-149-1-200807010-00006; www.ncbi.nlm.nih.gov