

Effectiveness and safety of metronidazole plus probiotics versus metronidazole alone in the treatment of bacterial vaginosis: randomized controlled trial

Mary Lee Roda Lim,¹ Lynnette Lasala^{1, 2, 3}

¹Department of Obstetrics and Gynecology, Southern Philippines Medical Center, JP Laurel Ave, Davao City, Philippines

²Metro Davao Medical and Research Center, JP Laurel Ave, Bajada, Davao City, Philippines

³Davao Medical School Foundation Hospital, Medical School Drive, Bajada, Davao City, Philippines

Correspondence

Mary Lee Roda Lim
mryllim@yahoo.com

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ABSTRACT

Background. Ingestion of probiotics can potentially restore the normal flora of the vagina and help in the treatment of bacterial vaginosis (BV).

Objective. To compare the effectiveness and safety of metronidazole plus probiotics versus metronidazole alone in treating women with BV.

Design. Open-label randomized controlled trial.

Setting. Outpatient Gynecology Clinic at Southern Philippines Medical Center in Davao City, Philippines.

Participants. 60 women 18-49 years old diagnosed to have BV by Nugent's criteria.

Intervention. Participants were randomized to receive either oral metronidazole 500 mg twice daily for 7 days, followed by oral probiotics one capsule once daily for 7 days, or oral metronidazole 500 mg twice daily for 7 days alone.

Main outcome measures. Cure rates two weeks after start of treatment; and recurrence rates within the succeeding 10 weeks after being cured from initial treatment.

Main results. The metronidazole alone (MA) group and metronidazole plus probiotics (MP) group were comparable in terms of demographic and clinical characteristics at baseline. After two weeks of treatment, cure rates were 22/30 (73.33%) in the MA group and 20/30 (66.67%) in the MP group ($p=0.8071$). Recurrence rate within three months was 5/22 (22.73%) in the MA group and 4/20 (20%) in the MP group ($p=0.8297$).

Conclusion. A metronidazole regimen with an added course of probiotics did not significantly differ from metronidazole alone in terms of BV cure rates two weeks after start of treatment and recurrence rates within 10 weeks after being cured.

Keywords. lactobacilli, Nugent's criteria, vaginal microbiota

INTRODUCTION

Bacterial vaginosis (BV) is the most common female genital infection caused by imbalance of vaginal microflora, accounting for a 28.56% prevalence rate in the Philippines among women aged 17-49 years old.¹ Among a nationally representative sample of women aged 14-49 years in the United States, the prevalence of BV in 2001-2004 was 29.2%.² The change in normal bacterial flora in the vagina, including reduction in or absence of lactobacilli, allows overgrowth of several pathogenic bacteria, and causes BV.³

Recommended treatment options for BV include oral and intravaginal antibiotics, such as metronidazole and clindamycin.⁴⁻⁶ The treatment of BV with antibiotics is not always effective due to resistance of the pathogens.⁷ Given the challenges of the current recommended treatment options, several studies have proposed the potential of ingested probiotics to aid in the treatment and prevent recurrence of BV.⁸ Topical⁹ and intravaginal administration of probiotics in the form of vaginal tablets¹⁰ or vaginal

suppositories¹¹ have been previously used to restore the normal vaginal flora. Ingested lactobacilli can potentially repopulate the vagina¹² by passing through the intestines, and colonizing the rectum before ascending to the vagina.¹³ Probiotics are expected to replenish the depleted lactobacilli that produce lactic acid and hydrogen peroxide,

IN ESSENCE

The management of bacterial vaginosis (BV) includes the administration of appropriate antibiotics and restoration of the normal vaginal microbiota.

In this study, cure rates and recurrence rates among patients with BV did not differ between those who received oral metronidazole alone and those who received oral metronidazole plus oral probiotics.

While ingested probiotics can potentially populate the vagina after colonizing the rectum, findings in this study do not support their addition to the antibiotic treatment of BV.



in order to maintain the vaginal pH, protect the vagina from opportunistic bacteria and prevent recurrence of infection.⁷ Several studies reported better cure rates and lesser recurrence of infection among patients with BV who were given probiotic supplements.^{5 14 15} We did the study because we wanted to know the effectiveness and safety of metronidazole plus a particular probiotic capsule preparation available in the market versus metronidazole alone in treating patients with BV and in preventing recurrence of the disease.

METHODS

Study design and setting

We did an open-label randomized controlled trial from October 2012 to March 2013 among women diagnosed to have BV at the Outpatient Gynecology Clinic at Southern Philippines Medical Center (SPMC), a tertiary hospital in Davao City, Philippines. The clinic caters to an average of 10,400 patients with gynecologic complaints per year.

Participants

Patients 18-49 years old diagnosed with BV by Nugent's criteria were eligible to participate in this study. The Nugent's criteria makes use of a scoring system that relies on findings of Gram staining of a cervico-vaginal smear.¹⁶ Three bacterial morphotypes are examined, counted and scored from the smear that is viewed under the microscope at a fixed magnification: *Lactobacillus* morphotype (large Gram-positive rods; scored 0 to 4; the lower the count, the higher the score), *Gardnerella* morphotype (small Gram-variable rods; scored 0 to 4; the higher the count, the higher the score), and *Mobiluncus spp.* morphotype (curved Gram-variable rods; scored 0 to 2; the higher the count, the higher the score).¹⁷ The individual morphotype scores are then added, and the total score (Nugent score) is interpreted against the following criteria: 0 to 3 (normal vaginal microflora), 4 to 6 (intermediate vaginal microflora), and 7 to 10 (bacterial vaginosis).¹⁸ In order to be eligible for this study, a patient must have a baseline Nugent score of 7-10.

Excluded from the study were patients with profuse vaginal bleeding and those who took antibiotics within two weeks prior to

initial assessment. To determine the adequate sample size for this study, we assumed that the cure rates for BV among those given metronidazole alone is 96%.¹⁹ Computations were made in order to detect a 25% difference in cure rates between the two groups. In a test for difference of two proportions carried out at a 95% level of confidence, a total sample size of 60 would have 80% power of rejecting the null hypothesis if the alternative holds. Figure 1 outlines the flow of patients during recruitment, randomization, follow-up, and analysis for this study.

Interventions and randomization

We randomly assigned patients to one of two treatment arms. The first group received metronidazole 500 mg alone, one tablet twice a day for seven days. The second group received metronidazole 500 mg one tablet twice a day for seven days, followed by oral probiotics, one capsule once a day for the next seven days. For the oral probiotics in this study, we used a commercially available preparation in capsule form. The capsule contains seven live bacteria, namely, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, *Bifidobacterium longum*, and *Bifidobacterium breve*. The total viable count per capsule is 100 million CFU.

Data collection

We collected baseline sociodemographic and clinical characteristics from the participants who were eventually included in our study. For sociodemographic data, we gathered information on patients' age, highest educational attainment, employment status, and household income. For clinical characteristics, we asked for the patients' parity, gravidity, past medical history, concomitant diseases, and signs and symptoms, and we noted the characteristics of their vaginal discharge on physical examination. We also recorded the patients' Nugent scores upon enrolment into the study.

The primary outcomes for this study were cure rate and recurrence rate. To determine cure status, we repeated the cervico-vaginal specimen collections and Nugent score measurements among all the patients who returned for follow-up at 2 weeks after start of treatment. Among those who were cured, we also repeated the

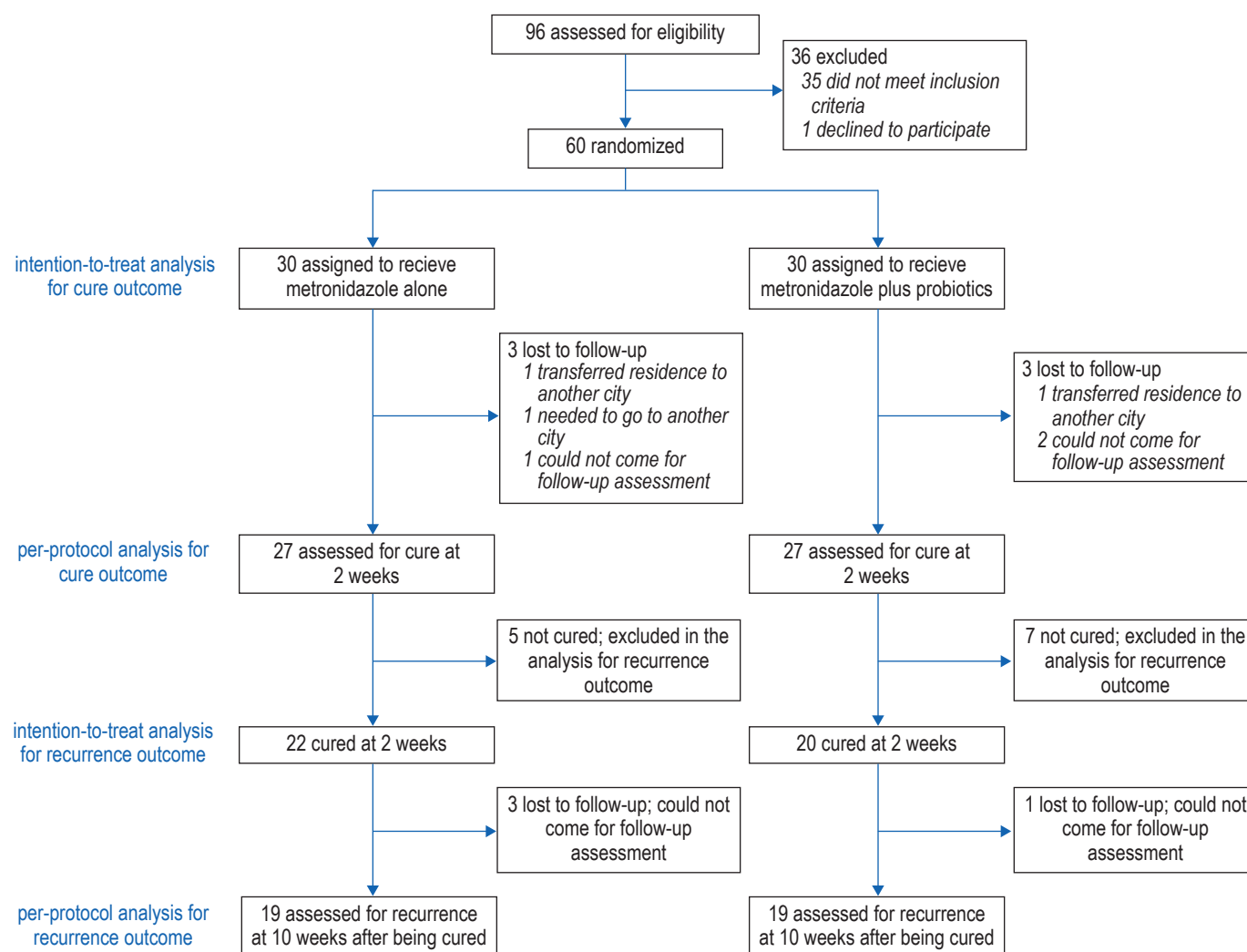


Figure 1 Screening, randomization, follow-up, and analysis of patients in the study.

specimen collections and Nugent score measurements on the 2nd and 10th weeks after being cured in order to determine recurrence status. Cure was considered when Nugent score 2 weeks after start of treatment was recorded to be ≤ 6 . Among those who were cured, we considered recurrence when Nugent score was recorded to be 7 to 10 anytime within 10 weeks after being cured. We also instructed the patients to report possible side effects of the interventions, such as symptoms of hypersensitivity, metallic taste, and gastrointestinal upset.

Statistical analysis

The primary analysis for this study was performed according to the intention-to-treat principle. The intention-to-treat population for the cure outcome included all

patients who were randomized to either of the treatment arms. For the recurrence outcome, the intention-to-treat population included patients who were cured at 2 weeks. Per-protocol analyses were done by excluding patients who were lost to follow-up and considering only patients who were actually assessed for cure or recurrence. To assess the robustness of the main results, we also did several sensitivity analyses by assuming different scenarios for the outcomes of patients who were lost to follow-up. We summarized continuous data using means \pm standard deviations and compared them using t-test. We summarized categorical data using frequencies and percentages and compared them using chi-square test. A two-tailed p-value of <0.05 was considered significant. All statistical tests were done using Epi Info 7.1.4.0.

Table 1 Baseline demographic and clinical characteristics

Characteristics	Metronidazole alone (n=30)	Metronidazole + probiotics (n=30)	p-value
Mean age \pm SD, years	33.0 \pm 8.1	31.6 \pm 10.6	0.5582
Mean gravidity \pm SD	2 \pm 2	2 \pm 2	0.5160
Mean parity \pm SD	2 \pm 2	2 \pm 2	0.5380
Educational attainment, frequency (%)			0.7807
Elementary	4 (13.33)	4 (13.33)	
High school	4 (13.33)	20 (66.67)	
College	22 (73.33)	6 (20.00)	
Employed, frequency (%)	15 (50.00)	8 (29.63)	0.1175
Mean household income \pm SD, Philippine pesos	7,933.33 \pm 5,421	7,550.00 \pm 8,335.00	0.8335
Past medical history, frequency (%)			
Genital warts	1 (3.33)	1 (3.33)	1.0000
Herpes simplex	0	2 (6.67)	0.1503
Gonorrhea	2 (6.67)	2 (6.67)	1.0000
Chlamydia infection	0	1 (3.33)	0.3132
Bacterial vaginosis	1 (3.33)	0	0.3132
Vulvovaginal candidiasis	2 (6.67)	3 (10.00)	0.6404
Concomitant disease, frequency (%)			
Diabetes mellitus	0	1 (3.33)	0.3132
Asthma	2 (6.67)	1 (3.33)	0.5537
Adnexal mass	2 (6.67)	2 (6.67)	1.0000
Uterine mass	3 (10.00)	6 (20.00)	0.2781
Signs and symptoms, frequency (%)			
Burning sensation	5 (16.67)	4 (13.33)	0.7177
Vulvar pruritus	5 (16.67)	8 (26.67)	0.3472
Dyspareunia	6 (20.00)	11 (36.67)	0.1520
Foul-smelling vaginal discharge	13 (43.33)	20 (66.67)	0.0693
Vulvar edema	1 (3.33)	0	0.3132
Vulvar excoriations	1 (3.33)	4 (13.33)	0.1611
Vulvar fissures	1 (3.33)	1 (3.33)	1.0000
Vaginal spotting	4 (13.33)	4 (13.33)	1.0000
Pelvic tenderness	2 (6.67)	0	0.1503
Vaginal discharge characteristics, frequency (%)			0.0762
Grayish	23 (76.67)	17 (56.67)	
Yellowish	7 (23.33)	9 (30.00)	
No discharge	0	4 (13.33)	

RESULTS

The 60 patients who were recruited into this trial were randomized either to the metronidazole alone (MA) group (n=30) or to the metronidazole plus probiotic (MP) group (n=30). The sociodemographic and clinical characteristics of the patients at baseline are shown in Table 1. The two treatment groups were comparable in terms of age, educational attainment, employment status, household income, obstetrical history, past medical history, concomitant diseases, signs and symptoms, and vaginal discharge characteristics at the start of the study.

Table 2 shows the cure rates and recurrence rates between the treatment arms and according to the type of analysis. There

were 27 patients from the MA group and another 27 patients from the MP group who returned for assessment of cure status two weeks after starting treatment. On intention-to-treat analysis, there was no significant difference between the cure rates in the MA group (22/30; 73.33%) and the MP group (20/30; 66.67%) ($p=0.8071$).

Among the patients who were cured, there were 19 patients from the MA group and another 19 patients from the MP group who could be assessed for BV recurrence within the subsequent 10 weeks after the cure assessment. On intention-to-treat analysis, the recurrence rates were 5/22 (22.73%) in the MA group and 4/20 (20.00%) in the MP group ($p=0.8297$).

Table 2 Clinical outcomes

Outcome	Metronidazole alone	Metronidazole + probiotics	p-value
Cure, frequency (%)†			
Intention-to-treat analysis	22/30 (73.33)	20/30 (66.67)	0.8071
Per-protocol analysis	22/27 (81.48)	20/27 (74.07)	0.5127
Recurrence, frequency (%)‡			
Intention-to-treat analysis	5/22 (22.73)	4/20 (20.00)	0.8297
Per-protocol analysis	5/19 (26.32)	4/19 (21.05)	0.7028

†Measured at two weeks after start of treatment; ‡measured within 10 weeks after being cured.

After doing per-protocol analyses and several sensitivity analyses, the cure and recurrence rates remained comparable between the two treatment groups.

One patient in the MP group developed pruritic rashes after taking metronidazole, hence, the antibiotic was discontinued on the 5th day, and the patient was given cetirizine 10 mg once a day for 5 days. The patient took the oral probiotics as scheduled. No other side effects of the interventions were noted in either of the groups.

DISCUSSION

Key results

We did this study in order to find out whether adding a 7-day course of oral probiotics to metronidazole treatment for BV would affect cure and recurrence rates. Both outcomes did not significantly differ between the metronidazole alone group and the metronidazole plus probiotics group.

Strengths and limitations

We were able to demonstrate that adding oral probiotics at a dose of 100 million CFU per day for 7 days to a metronidazole treatment regimen does not change cure and recurrence rates of BV. Follow-up rate was high among the study participants, and the study population had been adequate up to the last assessment of the outcomes. Our findings also remained unchanged across different analytical approaches (intention-to-treat, per-protocol, and sensitivity analyses).

There were some limitations in this study. We did not account for or monitor some factors that could possibly affect the outcomes that we measured, such as personal hygiene practices and vaginal pH. Hygiene practices in the vaginal area²⁰ and vaginal pH²¹ may affect the bacterial flora of the vagina, as well as the cure and recurrence

rates of BV. For this study, we only used the Nugent's criteria to screen patients for entry into the study and to measure the study outcomes. Using other diagnostic criteria for BV, such as the Amsel's criteria,²² the Spiegel criteria,²³ or the Ison-Hay classification,²⁴ in lieu of or in combination with Nugent's criteria may yield different outcome findings for this study.

Interpretation

Several trials on probiotic use among patients with BV demonstrated different results because of the varied therapeutic approaches employed in the trials.^{14 15 25-30} Most of the trials used antibiotic and probiotic combinations,^{14 15 25-27 30} but some used probiotics alone as treatment for bacterial vaginosis.^{28 29} As to route of administration of probiotics, some trials used the intravaginal route,^{15 25-27 30} while others used the oral route.^{28 30} In some trials, the probiotics were administered together with the antibiotics,^{14 15} while in others, the probiotics were administered after the antibiotic course.^{25 26} The doses of the probiotics used in the study also varied from 10 million CFU²⁷ to 1 billion CFU.^{14 25} Durations of probiotics administration ranged from 7 days²⁵ or one menstrual cycle,²⁶ to 6 months.³⁰ Finally, the lactobacilli strains used in the trials varied greatly, but many used *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus gasseri*, and *Lactobacillus acidophilus* alone or in different combinations.^{14 15 26-28 30}

The probiotic preparation in our study has been marketed for general use, rather than for specific use in gynecologic conditions. As such, it contains other good bacteria, including those that belong to the normal gastrointestinal microflora that were not utilized in previous studies on BV. The probiotic dose, route of administration, duration of administration, and the timing of administration of probiotics that we employed in our study were similar to those used in other studies. Like some clinical trials done previously,^{15 26 27} our study showed that adding probiotics to the antibiotic treatment regimen for BV does not provide any beneficial effects in terms of cure or prevention of recurrence.

Generalizability

We did this study among women with diverse sociodemographic characteristics,

and with clinical profiles that cover a wide range of past and concomitant diseases. The symptoms that our participants reported at baseline also include the most common signs and symptoms of BV. Hence, the results of this study can be applicable to most women diagnosed to have BV by Nugent's criteria. Our findings do not support the addition of oral probiotics to the antibiotic treatment regimen for BV. Treatment of BV with a week's course of oral metronidazole alone can result in a reasonably high cure rate two weeks after start of treatment and a reasonably low recurrence rate within 10 weeks of being cured of BV.

CONCLUSION

Among patients with BV by Nugent's criteria, oral metronidazole treatment did not significantly differ from oral metronidazole plus oral probiotics treatment in terms of cure two weeks after treatment and recurrence within 10 weeks after being cured of BV.

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Ethics approval

This study was reviewed and approved by the Department of Health XI Cluster Ethics Review Committee (DOH XI CERC reference P12072601).

Reporting guideline used

CONSORT Checklist (<http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Checklist.doc>)

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REFERENCES

1. Wi TEC, Sanieel OP, Ramos ER, MacNeil J, Neilsen G. RTI/STI Prevalence in selected sites in the Philippines. *Family Health International*; 2002.
2. Koumans E, Sternberg M, Bruce C, McQuillan G, Kendrick J, Sutton M et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. *Sex Transm Dis*. 2007;34(11):864-9.
3. Eschenbach DA. History and review of bacterial vaginosis. *Am J Obstet Gynecol*. 1993;169(2 Pt 2):441-5.
4. Centers for Disease Control and Prevention. Bacterial vaginosis treatment and care. Available at: <http://www.cdc.gov/std/bv/treatment.htm>. Accessed July 13, 2015.
5. Senok AC, Verstraeten H, Temmerman M, Botta GA. Probiotics for the treatment of bacterial vaginosis. *Cochrane Database Syst Rev*. 2009;(4):CD006289.
6. Ya W, Reifer C, Miller LE. Efficacy of vaginal probiotic capsules for recurrent bacterial vaginosis: a double-blind, randomized, placebo-controlled study. *Am J Obstet Gynecol*. 2010;203(2):120.e1-6.
7. Beigi RH, Austin MN, Meyn LA, Krohn MA, Hillier SL. Antimicrobial resistance associated with the treatment of bacterial vaginosis. *Am J Obstet Gynecol*. 2004;191(4):1124-9.
8. Shalev E. Ingestion of probiotics: optional treatment of bacterial vaginosis in pregnancy. *Isr Med Assoc J*. 2002;4(5):357-60.
9. Kovachev S, Vatcheva-dobrevski R. [Efficacy of combined 5-nitroimidazole and probiotic therapy of bacterial vaginosis: randomized open trial]. *Akush Ginekol (Sofia)*. 2013;52(3):19-26.
10. Donders GG, Van bulck B, Van de walle P, Kaiser RR, Pohlig G, Gonser S, et al. Effect of lyophilized lactobacilli and 0.03 mg estriol (Gynoflor®) on vaginitis and vaginosis with disrupted vaginal microflora: a multicenter, randomized, single-blind, active-controlled pilot study. *Gynecol Obstet Invest*. 2010;70(4):264-72.
11. Delia A, Morgante G, Rago G, Musacchio MC, Petraglia F, De leo V. [Effectiveness of oral administration of Lactobacillus paracasei subsp. paracasei F19 in association with vaginal suppositories of Lactobacillus acidophilus in the treatment of vaginosis and in the prevention of recurrent vaginitis]. *Minerva Ginecol*. 2006;58(3):227-31.
12. Cribby S, Taylor M, Reid G. Vaginal microbiota and the use of probiotics. *Interdiscip Perspect Infect Dis*. 2008;2008:256490.
13. Morelli L, Zonenenschain D, Del piano M, Cognein P. Utilization of the intestinal tract as a delivery system for urogenital probiotics. *J Clin Gastroenterol*. 2004;38(6 Suppl):S107-10.
14. Anukam K, Osazuwa E, Ahonkhail I, Ngwu M, Osemene G, Bruce AW, et al. Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14: randomized, double-blind, placebo controlled trial. *Microbes Infect*. 2006;8(6):1450-4.
15. Larsson PG, Stray-pedersen B, Rytting KR, Larsen S. Human lactobacilli as supplementation of clindamycin to patients with bacterial vaginosis reduce the recurrence rate; a 6-month, double-blind, randomized, placebo-controlled study. *BMC Womens Health*. 2008;8:3.
16. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol*. 1991;29(2):297-301.
17. Sha BE, Chen HY, Wang QJ, Zariffard MR, Cohen MH, Spear GT. Utility of Amsel criteria, Nugent score, and quantitative PCR for Gardnerella vaginalis, Mycoplasma hominis, and Lactobacillus spp. for diagnosis of bacterial vaginosis in human immunodeficiency virus-infected women. *J Clin Microbiol*. 2005;43(9):4607-12.
18. Verstraeten H, Verhelst R. Bacterial vaginosis: an update on

- diagnosis and treatment. *Expert Rev Anti Infect Ther*. 2009;7(9):1109-24.
19. Greaves WL, Chungafung J, Morris B, Haile A, Townsend JL. Clindamycin versus metronidazole in the treatment of bacterial vaginosis. *Obstet Gynecol*. 1988;72(5):799-802.
 20. Bahram A, Hamid B, Zohre T. Prevalence of bacterial vaginosis and impact of genital hygiene practices in non-pregnant women in Zanjan, Iran. *Oman Med J*. 2009;24(4):288-93.
 21. Frobenius W, Bogdan C. Diagnostic Value of Vaginal Discharge, Wet Mount and Vaginal pH - An Update on the Basics of Gynecologic Infectiology. *Geburtshilfe Frauenheilkd*. 2015;75(4):355-366.
 22. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *Am J Med*. 1983;74(1):14-22.
 23. Spiegel CA, Amsel R, Holmes KK. Diagnosis of bacterial vaginosis by direct gram stain of vaginal fluid. *J Clin Microbiol*. 1983;18(1):170-7.
 24. Ison CA, Hay PE. Validation of a simplified grading of Gram stained vaginal smears for use in genitourinary medicine clinics. *Sex Transm Infect*. 2002;78(6):413-5.
 25. Petricevic L, Witt A. The role of *Lactobacillus casei rhamnosus* Lcr35 in restoring the normal vaginal flora after antibiotic treatment of bacterial vaginosis. *BJOG*. 2008;115(11):1369-74.
 26. Eriksson K, Carlsson B, Forsum U, Larsson PG. A double-blind treatment study of bacterial vaginosis with normal vaginal lactobacilli after an open treatment with vaginal clindamycin ovules. *Acta Derm Venereol*. 2005;85(1):42-6.
 27. Bradshaw CS, Pirota M, De Guingand D, Hocking JS, Morton AN, Garland SM, et al. Efficacy of oral metronidazole with vaginal clindamycin or vaginal probiotic for bacterial vaginosis: randomised placebo-controlled double-blind trial. *PLoS ONE*. 2012;7(4):e34540.
 28. Vujic G, Jajac Knez A, Despot Stefanovic V, Kuzmic Vrbanovic V. Efficacy of orally applied probiotic capsules for bacterial vaginosis and other vaginal infections: a double-blind, randomized, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2013;168(1):75-9.
 29. Facchinetti F, Dante G, Pedretti L, Resasco P, Annessi E, Doderio D. [The role of oral probiotic for bacterial vaginosis in pregnant women. A pilot study]. *Minerva Ginecol*. 2013;65(2):215-21.
 30. Marcone V, Rocca G, Lichtner M, Calzolari E. Long-term vaginal administration of *Lactobacillus rhamnosus* as a complementary approach to management of bacterial vaginosis. *Int J Gynaecol Obstet*. 2010;110(3):223-6.