ORIGINAL RESEARCH ARTICLE

Effectiveness of oral probiotics and metronidazole compared with oral probiotics and metronidazole pessaries in the treatment of bacterial vaginosis in Chinese women

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Abstract

Chinese guidelines recommend oral or metronidazole pessaries for treating bacterial vaginosis (BV). Although oral metronidazole has high bioavailability, it often causes adverse effects, which may be minimized by using the pessaries. This study compared the effectiveness, adverse effects, and recurrence rates between two groups of women receiving oral probiotics plus 200 mg metronidazole pessaries and those receiving oral probiotics plus 400 mg oral metronidazole. Women with BV were treated for 7 days with either regimen for one month. Both groups showed significant improvement in vaginal pH and Nugent scores ($p < 0.0001$), with greater improvement in vaginal pH in the pessary group. Oral metronidazole was associated with side effects, including metallic taste, headache, dizziness, and gastrointestinal disturbances, while pessaries caused vulvar itching. Recurrence at 12 months was lower in the pessary group compared to the oral group (24% vs. 37%, $p = 0.0105$). We conclude that probiotics combined with metronidazole (especially in pessary form) showed effective treatment outcomes with manageable side effects in Chinese women with BV. *(Afr J Reprod Health 2025; 29 [4]: 78-88).*

Keywords: Anti-anaerobes; Bacterial vaginosis; Metronidazole; Nugent score; Pessaries; Probiotic; Vaginal pH.

Résumé

Les directives chinoises recommandent les pessaires oraux ou métronidazole pour traiter la vaginose bactérienne (BV). Bien que le métronidazole oral ait une biodisponibilité élevée, il provoque souvent des effets indésirables, qui peuvent être minimisés par l'utilisation de pessaires. Cette étude a comparé l'efficacité, les effets indésirables et les taux de récidive entre deux groupes de femmes recevant des probiotiques oraux plus 200 mg de métronidazole et des pessaires de métronidazole et celles recevant des probiotiques oraux plus 400 mg de métronidazole oral. Les femmes atteintes de VB ont été traitées pendant 7 jours avec l'un ou l'autre régime pendant un mois. Les deux groupes ont montré une amélioration significative du pH vaginal et des scores de Nugent ($p < 0,0001$), avec une plus grande amélioration du pH vaginal dans le groupe pessaire. Le métronidazole oral était associé à des effets secondaires, notamment un goût métallique, des maux de tête, des étourdissements et des troubles gastro-intestinaux, tandis que les pessaires provoquaient des démangeaisons vulvaires. La récidive à 12 mois était plus faible dans le groupe pessaire par rapport au groupe oral (24 % contre 37 %, $p = 0,0105$). Nous concluons que les probiotiques associés au métronidazole (en particulier sous forme de pessaire) ont montré des résultats thérapeutiques efficaces avec des effets secondaires gérables chez les femmes chinoises atteintes de VB. *(Afr J Reprod Health 2025; 29 [4]: 78-88).*

Mots-clés: Anti-anaérobies ; Vaginose bactérienne ; Métronidazole ; Score de Nugent ; Pessaires ; Probiotique ; pH vaginal

Introduction

In the female lower genital tract, bacterial vaginosis is the common female urogenital system infection among females of reproductive ages and is correlated with worse health outcome[1]. Bacterial vaginosis generally occurs due to a decrease in lactobacilli and an increase in anaerobic bacteria[2]. The global prevalence rate is 23–29 %[1] while in Chinese women rate is about 30 %[3]. Bacterial vaginosis has higher incidence in the reproductive age, and also associated with increases complications in pregnancy[2]. Women with bacterial vaginosis often complain of leukorrhea (vaginal

white discharge), vulvar itching, vaginal odor, and burning pain[4]. About 50 % of women with the infection are asymptomatic [3].

The Chinese guidelines recommend oral or topical anti-anaerobes (e.g. metronidazole) for symptomatic or asymptomatic treatment of bacterial vaginosis in pregnant and non-pregnant women[5]. In addition, the replacement of *Lactobacillus* spp. with anaerobic bacteria (e.g., *Gardnerella* spp., *Prevotella* spp., *Mobiluncus* spp., and *Atopobium vaginae*) are reported effective in bacterial vaginosis because of high production of cadaveric amines, succinate, utrescine, and acetate by anaerobic bacteria leading to change chemical compositions of *Lactobacillus* spp. and improved pH of vagina[6]. Vaginal flora and vaginal pH are different from race to race[7].

The oral bioavailability of metronidazole is high 98.9 % [8]. However, oral metronidazole has adverse events like headache, dizziness, nausea, stomach upset, loss of appetite, vomiting, constipation, metallic taste in the mouth, and diarrhea[9]. By using vaginal pessaries, it is possible to increase the contact time of the drug, decrease adverse effects, and obtain multiple benefits while avoiding adverse effects[10].

This study is designed to evaluate the effectiveness (vaginal pH and Nugent score), adverse effects (unwanted effects during one month of treatment and of 6-months of follow-up), and recurrences (during 12-months of follow-up) among women who received oral probiotics plus 200 mg metronidazole pessaries against those of women who received oral probiotics plus oral 400 mg metronidazole in the treatment of bacterial vaginosis in the Western region of China.

Methods

Study design

A retrospective study conducted from data of Chinese women at the Xi'an People's Hospital (Xi'an Fourth Hospital), Xi'an City, China.

Inclusion criteria

Women (aged 18 years or more, with Nugent score 7 or more) who had complained of vaginal discharge, vulvar itching, vaginal odor, and/ or vaginal burning pain were included in the study.

Exclusion criteria

Women with incomplete data were excluded from the study.

Sample size calculation

The study was based on the assumption that after treatment there would be no more than 50 % and no less than 15 % of recurrence in women who received treatment for bacterial vaginosis as compared to before-treatment conditions [6]. Based on this assumption and $\alpha = 0.05$, and $\beta = 0.1$, the same size calculated was 100. The sample size was calculated using OpenEpi, Software, USA (online version).

Cohorts

A total of 109 women with bacterial vaginosis received oral 400 mg metronidazole tablet twice a day for one week and oral probiotics containing L. gasseri TM13 and L. crispatus LG55 [11] for one month (OPM cohort). In contract, a total of 136 women with bacterial vaginosis received 200 mg metronidazole pessaries every day for 7 days [2] with oral probiotics containing L. gasseri TM13 and L. crispatus LG55 [11] for one month (BNS cohort).

Follow-up visits were made every 15 days for 6 months after the start of treatment.

Outcome measures

Demographic and clinical parameters

Demographic and clinical parameters of women were collected from hospital records and analyzed.

Sexual meeting

Self-reported sexual meetings with a partner were noted.

Pathological confirmation

A vaginal smear was prepared. It was observed under a microscope and confirmation of bacterial vaginosis was made after pathology.

Vaginal pH

Clinical testing was done for vaginal pH.

Nugent score

Vaginal bacterial gram-positive rods were calculated. A score of 0–10 is generated from combining large Gram-positive rods (Lactobacillus

morphotypes; 0 to 4 score), small Gram-variable rods (Gardnerella vaginalis morphotypes; 0 to 4 score), and curved Gram-variable rods (Mobiluncus spp. morphotypes; 0 to 2 score). A score of 7 or more was considered as bacterial vaginosis[12].

Adverse effects

Any unwanted effects during one month of treatment and of 6-months of follow-up were considered as adverse effects. Treatment of metronidazole was only for 7 days. None of the women showed manifestations of abnormal liver or kidney functions. Therefore, laboratory tests, such as liver and kidney function tests, and blood routine results were not performed further.

Recurrence

Complaints of vaginal discharge, vulvar itching, vaginal odor, and/ or vaginal burning pain within 12 months of follow-up after treatment were considered as recurrence [13].

Clinical benefits for treatment of bacterial vaginosis

The clinical benefits of treatment of bacterial vaginosis in women were evaluated as a function of the beneficial scores. Beneficial scores for treatment of bacterial vaginosis in women were calculated from the risk of recurrence, as expressed in Eq. (1). The risk of recurrence was defined by a calculation that involved the incidence of recurrence of bacterial vaginosis in women who underwent treatment (Eq. (2)). The beneficial score of the treatment of bacterial vaginosis is the area above the curve of the treatment adopted, and the working area is the area under the curve of the treatment adopted. For all adopted treatments, 15 % or less of differences in the incidence of recurrence of women were used as the reference standard [14, 15].

$$\text{Beneficial score} = \frac{\text{Number of women without recurrence}}{\text{Total number of women}} - \left(\frac{\text{Number of women with recurrence}}{\text{Total number of women}} \times \text{Risk of recurrence}\right) \quad (1)$$

$$\text{Risk of recurrence} = \frac{\text{Percentages of women with recurrence}}{\text{Percentages of women with recurrence}+15} \quad (2)$$

Statistical analyses

InStat 3.01, GraphPad Software, San Deigo, CA, USA was used for statistical analysis purposes. The normality of continuous variables was evaluated using the Kolmogorov and Smirnov methods. Normal continuous, categorical, and non-normal continuous variables are depicted as mean ± standard deviation (SD), frequencies with percentages in parenthesis, and median with Q3–Q1 in parenthesis, respectively. Categorical variables were subjected to the Fisher's exact test or Chi-square test (χ2-test (with Yates correction)) for statistical analysis. Mann–Whitney test (between cohorts) or Friedman test (within cohort) was used for statistical analysis of non-normal continuous variables. Dunn's multiple comparisons test was used for post hoc analysis for non-normal continuous variables. All results were considered significant if the p-value was less than 0.05.

Ethical considerations

This study was approved by the Ethics Committee of Xi 'an People's Hospital, and all patients involved in this study obtained and signed informed consent. Allprocedures involving human participants in the research were performed in accordancewith the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable standards.

Results

Study population

From 17 January 2020 to 1 February 2021, a total of 261 women were available with complaints of vaginal discharge, vulvar itching, vaginal odor, and/ or vaginal burning pain at the department of Gynecology and Obstetrics of the Xi'an People's Hospital (Xi'an Fourth Hospital), Xi'an City, China and the referring hospitals. Among them (data of 261 women) complete data of 16 women were not available in hospital records.

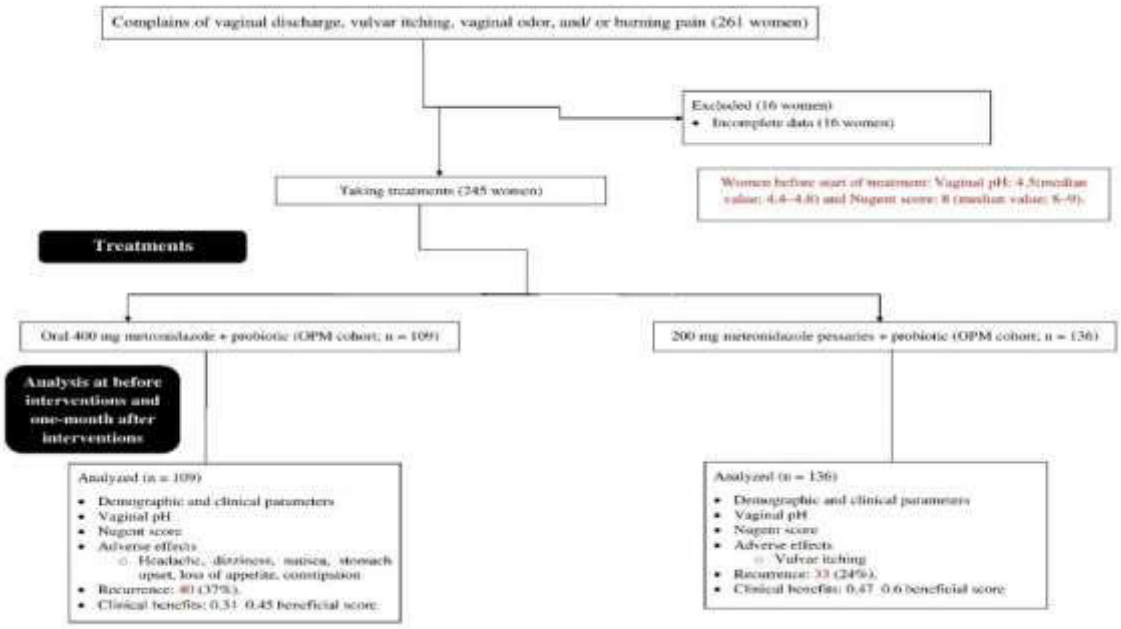

Figure 1: Flow diagram of the study. The red color indicates worse outcomes.

Therefore, these women were excluded from the study. Demographic and clinical parameters, pathological examinations, vaginal pH, Nugent score, adverse effects, and recurrences of 245 women were included in the analyses. The retrospective flow diagram of the study is presented in Figure 1.

Demographic and clinical parameters

Women were 28 years (median value; 19–42 years) old, mostly Han Chinese, and had a 24.5 kg/ m^2 (median value; 24–27 kg/ m^2) body mass index. Two-thirds of women were married. More than 80 % of women had vulvar itching. Besides vulvar itching, women had complained of vaginal discharge, vaginal odor, and vaginal burning pain. Women had occasional sexual meetings with partners. Vaginal pH was 4.5 (median value; range: 4.4–4.8) and Nugent score was 8 (median value; range: 8–9). The details of the demographic and clinical parameters of women before the start of treatment are reported in Table 1.

Df: Degree of freedom, N/A: not applicable, CI: Confidence interval (using the approximation of Katz. For categorical variables).

Women had one or more clinical symptoms.

Categorical and non-normal continuous variables are depicted as frequencies with percentages in parenthesis and median with Q3–Q1 in parenthesis, respectively.

All results were considered significant if the *p*-value was less than 0.05.

Test value (Mann–Whitney U-statistic for Mann–Whitney test; χ^2-statistics for χ^2-test).

Outcome measures

In the OPM and BNS cohorts, the vaginal pH and Nugent scores of women were improved after one month of treatment (AT) as compared to before-treatment (BT) conditions. Vaginal pH was improved more in women of the BNS cohort than those of women of the OPM cohort. In the AT conditions, Nugent score was statistically similar between both cohorts. The details of outcome measures of women with BT and AT conditions are reported in Table 2.

BT: Before the start of treatment, AT: After one month of treatment. Variables are depicted as median with Q3–Q1 in parenthesis.

All results were considered significant if the *p*-value was less than 0.05.

Table 1: Demographic and clinical parameters of women before the start of treatment

Parameters	Cohorts		Comparisons between cohorts			
	OPM	BNS				
Treatment	Oral 400 mg metronidazole + probiotic	200 mg metronidazole pessaries + probiotic				
Numbers of women	109	136	*p*-value	Df	Test value	95%CI
Age (years)	28(32–25)	28(31–25)	0.7653	N/A	7,247	N/A
Ethnicity						
Han Chinese	100(92)	127(93)	0.9711	3	0.2388	N/A
Mongolian	7(6)	7(5)				
Tibetan	1(1)	1(1)				
Uyghur Muslim	1(1)	1(1)				
Body mass index (kg/ m^2)	25.5(26–24.5)	26(26.5–25)	0.0694	N/A	6536	N/A
Marital status						
Married	80(73)	100(74)	0.981	1	0.0006	0.7260 to 1.367
Unmarried/ Single	29(27)	36(26)				
Clinical symptoms						
Vaginal discharge	45(41)	45(33)	0.792	3	1.038	N/A
Vulvar itching	101(93)	105(77)				
Vaginal odor	55(50)	45(33)				
Burning pain	37(34)	38(28)				
Sexual meetings in a week	0(1–0)	0(1–0)	0.4791	N/A	7,028	N/A
Vaginal pH	4.5(4.6–4.5)	4.5(4.6–4.5)	0.1127	N/A	6,544	N/A
Nugent score	8(9–8)	8(9–8)	0.0549	N/A	6,396	N/A

Table 2: Outcome measures of women after one month of treatment

Characters	Cohorts								Comparisons between cohorts in AT conditions	
	OPM				BNS					
Therapy	Oral 400 mg metronidazole + probiotic				200 mg metronidazole pessaries + probiotic					
Women	109	109			136	136				
Level	BT	AT	#*p*-value	#Test value	BT	AT	#*p*-value	#Test value	*p*-value	Test value
Vaginal pH	4.5(4.6–4.5)	4.2(4.3–4.1)	<0.001	161	4.5(4.6–4.5)	4(4.1–4)	<0.001	219	<0.001	303
Nugent score	8(9–8)	6(6–6)	<0.001	194	8(9–8)	6(6–6)	<0.001	245	>0.05	305

Table 3: Adverse effects during one month of treatment and of 6-months of follow-up

Event	Cohorts		Comparisons between cohorts		
	OPM	BNS			
Treatment	Oral 400 mg metronidazole + probiotic	200 mg metronidazole pessaries + probiotic			
Numbers of women	109	136	*p*-value	Relative risk	95%CI
Headache	7(6)[$]	0(0)	0.004	2.248	1.954 to 2.585
Dizziness	11(10)[$]	0(0)	0.0001	2.388	2.053 to 2.777
Nausea	25(23)[$]	1(1)	<0.0001	2.507	2.084 to 3.015
Stomach upset	17(16)[$]	1(1)	<0.0001	2.33	1.921 to 2.828
Loss of appetite	47(14)[$]	1(1)	<0.0001	3.111	2.521 to 3.839
Vomiting	2(2)	0(0)	0.1969	2.271	1.971 to 2.617
Constipation	8(7)[$]	0(0)	0.0013	2.347	2.024 to 2.720
Metallic taste in the mouth	109(100)[$]	0(0)	<0.0001	Infinity	-Infinity to Infinity
Diarrhea	2(2)	0(0)	0.1969	2.271	1.971 to 2.617
Vulvar itching	0(0)	15(11)[#]	0.0002	0	-Infinity to Infinity

Table 4: Clinical benefits for treatment of bacterial vaginosis.

% Recurrences	Cohorts (beneficial score)	
	OPM	BNS
Treatment	Oral 400 mg metronidazole + probiotic	200 mg metronidazole pessaries + probiotic
Numbers of women	109	136
0	0.63	0.76
5	0.54	0.68
10	0.49	0.63
20	0.42	0.57
40	0.37	0.52
50	0.35	0.51
60	0.34	0.50
70	0.33	0.49
80	0.32	0.49
90	0.32	0.48
100	0.31	0.48
Clinical benefit	0.31–0.45 beneficial score	0.47–0.6 beneficial score
Risk of undertreatment	<0.31 beneficial score	<0.47 beneficial score
Risk of recurrence	>0.45 beneficial score	>0.6 beneficial score

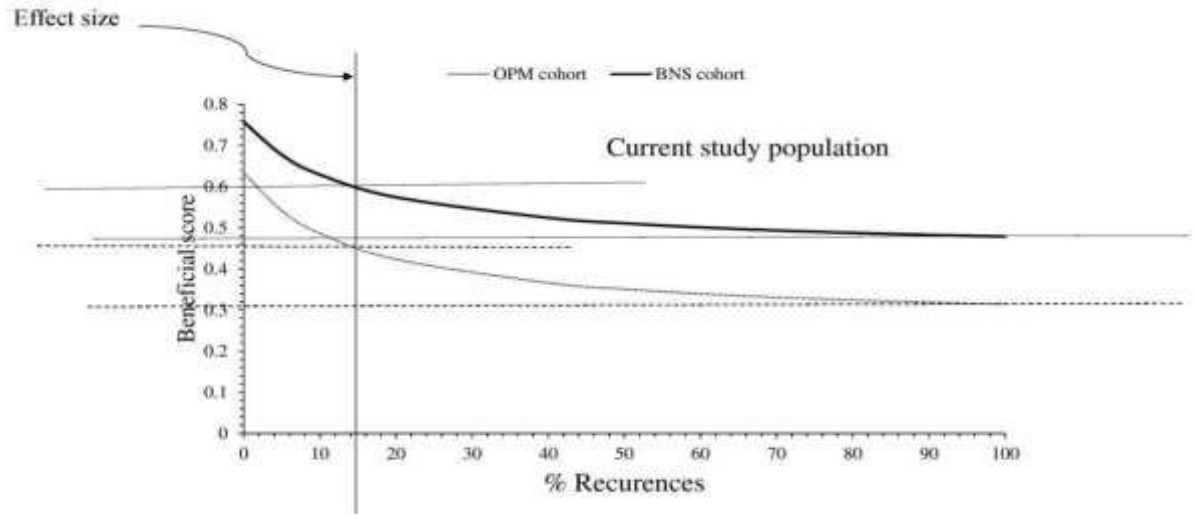

Figure 2: Graphical presentations of clinical benefits for treatment of bacterial vaginosis.

Table 5: Results of assumptions test adopted in the study

Variables	Adopted test with reasons
Categorical variables	
2×2 Tables	Fisher exact test or Chi-square test (with Yates correction; if the sample size is more than 50 and the individual sample number is 5 or more)
Large tables	Chi-square test
Continuous variables	
Demographic and clinical parameters of women before the start of treatment	
Age (years)	Normality test values (p = 0.0178; 0.0338) failed in the normality test, i.e. Mann-Whitney test
Body mass index (kg/ m^2)	Normality test values (p = 0.004; 0.0001) failed in the normality test, i.e. Mann-Whitney test
Sexual meeting in a week, vaginal pH, and Nugent score	Normality test values ($p < 0.0001$ for both) failed in the normality test, i.e. Mann-Whitney test
Outcome measures of women after one month of treatment	
Vaginal pH and Nugent score (within cohort)	All columns failed in the normality test ($p < 0.0001$ for all), i.e. Friedman test.
Vaginal pH and Nugent score (between cohorts)	All columns failed in the normality test ($p < 0.0001$ for all), i.e. Mann-Whitney test.

Table 6: Comparative studies on the treatment of bacterial vaginosis in different settings

Study	Published year	Women ethnicity	Sample size (N; women)	Age (years)	Follow-up	Women with recurrences
Controlled trial, Qi et al.[2]	2023	Chinese	67(33; 34)	18–55	3-months	Not applicable
Prospective study, Zhang *et al.*[3]	2022	Han Chinese	3,420	Reproductive age	4-months	Not applicable
Prospective study, Watkins *et al*.[9]	2024	North American	114,313	12–49	≥12 months	49,611/114,313
Longitudinal study, Chen *et al.*[16]	2021	Chinese	60	23–61	1 year	Not applicable
Pilot study, Martoni *et al*.[17]	2022	Denish	36(24; 12 women)	18–50	42 days	Not applicable
Clinical study, Reznichenko *et al.*[18]	2020	Ukraine	164(82 women each)	18–45	120 days	42/164
Case–control study[19]	2016	Itali	250(125; 125)	>18 years	9 months	Low rate
Controlled trial, Husain *et al*·[20]	2020	English	304(152 women each)	>16 years	15 weeks	Not applicable
Retrospective cohort study *et al*. Delfstra [21]	2023	Netherlands	441 women	>18 years	12-months	91/441

Mann–Whitney test (between cohorts) or Friedman test (within cohort) was used for statistical analysis and Dunn's multiple comparisons test was used for *post hoc* analysis.

Test value (Mann–Whitney U-statistic for Mann-Whitney test; Friedman Statistic for Friedman-test). #Comparisons between BT and AT.

Adverse effects

Oral 400 mg metronidazole tablets had a metallic taste in the mouth of all women of the OPM cohort. In addition, oral 400 mg metronidazole tablets caused headache, dizziness, nausea, stomach upset, loss of appetite, and constipation in women of the OPM cohort during one month of treatment and 6-months of follow-up period.

However, those who received pessaries in the BNS cohort reported vulvar itching during one month of treatment and of 6-months of follow-up in women. The details of unwanted effects are presented in Table 3.

Variables are depicted as frequencies with percentages in parentheses.

Fisher's exact test was used for statistical analysis.

CI: Confidence interval (using the approximation of Katz.). All results were considered significant if the *p*-value was less than 0.05.

[$]Significant adverse effects due to oral 400 mg metronidazole.

[#]Significant adverse effects due to pessaries.

Recurrence

During 12 months of follow-up 40 (37 %) women from the OPM cohort and 33 (24 %) women from the BNS cohort had reported recurrence. Fewer numbers of women reported recurrence in the 12 months of follow-up in the BNS cohort than those of the OPM cohort ($p = 0.0105$, degree of freedom: 1, Chi-square statistic (with Yates correction) = 6.552; χ^2-test).

Clinical benefits of treatment of bacterial vaginosis

Clinical benefits for women in the OPM cohort had a 0.31–0.45 beneficial score and that of women in the BNS cohort had a 0.47–0.6 beneficial score. Both treatments would have the risk of recurrences and women of the OPM cohort had a higher risk of

recurrences than women of the BNS cohort. The graphical presentations of the clinical benefits of the treatment of bacterial vaginosis are reported in Fig. 2. Both treatments would have a decrease in the beneficial score with an increase in % recurrences (up to 50 % or more). The details of the clinical benefits for the treatment of bacterial vaginosis are reported in Table 4 /fig2 The results of the assumption test are presented in Table 5

Discussion

The results of this study indicate that more than 80 % of the women had vulvar itching. Other causes of itching include vulvar candidiasis, desquamative inflammatory vaginitis, and vaginal atrophy. Only bacterial vaginitis has valvular itching and vaginal pH 4.5. Therefore all women were treatment with metronidazole and more numbers of women have valvular itching.

Nugent score was improved in women of both cohorts and statistically similar between both cohorts in AT condition. Probiotics modulate vaginal flora in bacterial vaginosis[2,16,17]. The results of Nugent score in AT condition of women for bacterial vaginosis are consistent with those of controlled trials[2,18] and case–control study [19] but not consistent with those of another controlled trial[20]. The sample size was responsible for these contradictory results. Oral administration of probiotics containing L. *gasseri* TM13 and L. *crispatus* LG55 for one month with 7 days of metronidazole (oral or pessaries) is effective in Chinese women with bacterial vaginosis.

Women in the BNS cohort had improved vaginal pH, Nugent score, fewer numbers of women with recurrence in the 12 months of follow-up, and higher beneficial scores for treatment than those of women of the OPM cohort. Bacteria in vaginosis develop biofilm that is refractory to oral metronidazole[13]. The results of recurrences of women for bacterial vaginosis are consistent with those of a retrospective cohort study[21] and case–control study[19]. Metronidazole vaginal pessaries with probiotics in women with bacterial vaginosis provide better treatment to women for bacterial vaginosis and decrease the risk of recurrences of bacterial vaginosis.

Both treatments would have the risk of recurrences and recurrences of bacterial vaginosis are reported in a total of 73 (30 %) of women who received metronidazole (oral or pessaries) with probiotics. The results of occurrences of recurrences of the total enrolled women for bacterial vaginosis are consistent with those of a retrospective cohort study[21,] case–control study[19], and prospective study[9]. Metronidazole treatment is debatable for bacterial vaginosis[22]. In addition, a total of 68 % of isolated strains of *Gardnerella vaginalis* are reported resistant to metronidazole[21]. In addition, there would be chances of 400 mg oral dose of metronidazole instead of 500 mg oral metronidazole responsible for recurrences. Metronidazole treatment may have limited efficacy in bacterial vaginosis.

The details of comparative studies on the treatment of bacterial vaginosis in different settings are presented in Table 6.

There are several limitations of the study, for example, The study's retrospective design and independent parameters for bacterial vaginosis are not evaluated. The treatment prescribed for partners was not reported or discussed. After the start of treatment and in follow-up data of sexual meetings with partners were not reported.

The oral dose of metronidazole used in the control group in the current study was fewer (oral probiotics plus oral 400 mg metronidazole for bacterial vaginosis) and the standard evidence-based treatment of oral 500 md metronidazole that is usually used across the world [19]. The possible justification for the same is that in our institute oral probiotics plus oral 400 mg metronidazole is prescribed for bacterial vaginosis (institutional protocol, not published yet). Moreover, oral probiotics plus oral 400 mg metronidazole and oral probiotics plus oral 500 mg metronidazole for bacterial vaginosis are equally effective.

In conclusion, oral administration of probiotics containing L. *gasseri* TM13 and L. *crispatus* LG55 for one month with 7 days of metronidazole (oral or pessaries) is effective in Chinese women with bacterial vaginosis. Metronidazole vaginal pessaries with probiotics in women with bacterial vaginosis provide better treatment to women for bacterial vaginosis and decrease the risk of

recurrences of bacterial vaginosis. Metronidazole treatment may have limited efficacy in bacterial vaginosis.

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Consent to publications

Not applicable.

Availability of data and materials

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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Conflict of interest

The authors declare that they have no conflicts of interest or any other competing interests regarding the results and/or discussion reported in the research.

Authors' contributions

Both authors have read and approved the manuscript for publication. MZ was the project administrator and contributed to the conceptualization, data curation, investigation, supervision, resources, methodology, validation, and literature review of the study. JW contributed to resources, methodology, formal analysis, methodology, software, visualization, and literature review of the study and drafted and edited the manuscript for intellectual content. Both authors agree to be accountable for all aspects of the work, ensuring its integrity and accuracy. MZ and JW confirmed the authenticity of the raw data.

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