Vaginal Suppository of Metronidazole (750 mg) plus Miconazole Nitrate (200 mg) versus Oral Metronidazole (2 g) for Bacterial Vaginosis: A Randomized Controlled Trial

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ABSTRACT

Objective: To compare the cure rates, side effects, satisfaction, and recurrence rates of bacterial vaginosis (BV) in women having vaginal suppository of metronidazole (750 mg) plus miconazole (200 mg) - the "NPF group" - versus oral metronidazole (2 g) - the "MET group."

Materials and Methods: This September 2019–March 2020 trial enrolled symptomatic women aged 18-45 years diagnosed with BV based on Amsel's criteria. Excluded were women who were immunocompromised; allergic to metronidazole or miconazole; had BV episodes during the preceding 3 months; or had abnormal vaginal bleeding. After randomization with a ratio 1:1, another vaginal swab was done for Nugent scoring. Two weeks later, the evaluation using Amsel's criteria and Nugent scores was repeated. Also, symptom resolution, side effects and satisfaction were evaluated. Symptomatic resolution referred to 75% improvement in discharge, irritation, itching, odor, and coital pain. At one and three months, subjective symptomatic recurrence was assessed by telephone.

Results: Data on 70 participants were analyzed (NPF, N=34; MET, N=36). Their average age was 32.3±7.9 years (NPF, 34.1±8.1; MET, 30.6±7.3). Without statistical significance, NPF had higher symptom resolution (67.7% vs 58.3%; P=0.420), cure rate by Amsel criteria (82.4% vs 77.8%; P=0.632), and cure rate by Nugent scoring (35.3% vs 16.9%; P=0.075). Both groups reported high satisfaction (NPF, 8.5±1.4; MET, 7.9±2.0; P=0.125). Side effects were comparable, including appetite loss, metallic taste, nausea, and dizziness.

Conclusion: For BV treatment, both vaginal suppository containing metronidazole (750 mg) plus miconazole nitrate (200 mg) and oral metronidazole (2 g) show comparable efficacy and side effects.

Keywords: Bacterial vaginosis; metronidazole; vaginal tablet (Siriraj Med J 2021; 73: 644-651)

INTRODUCTION

Bacterial Vaginosis (BV) is the most common cause of abnormal vaginal discharge in women of childbearing age.[1] It is a polymicrobial clinical syndrome characterized by a profound change in vaginal microbiota from a *Lactobacillius*- dominant state to anaerobic bacteria of high diversity including *Gardnerella vaginalis, Atopobium vaginae, Mobiluncus spp, Prevotella spp*, and

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other BV-associated bacteria (BVAB).[2,3] This change is accompanied by a rise in vaginal pH and increased amines which produce typical odor. BV increases the incidence of gynecologic and obstetric diseases, including of spontaneous abortion, premature labour, chorioamnionitis, and postpartum endometritis and pelvic inflammatory disease (PID).[4,5] Also, it associates with a 2-3 fold increased risk of acquiring sexually transmitted diseases (STDs) such as chlamydial infection, gonorrhea, genital herpes and human immunodeficiency virus (HIV) infection.[6-8]

The recommended treatment is metronidazole or clindamycin.[9] In Thailand, oral metronidazole is more commonly prescribed for BV. However, the metronidazole 400 mg oral tablet taken thrice a day commonly elicits adverse events such as a metallic taste, nausea and vomiting resulting in poor compliance.[10] A single oral dose of metronidazole 2gm has comparable efficacy with a 7-day course[10] and previous studies demonstrated less gastrointestinal side effects.[11-13] Therefore, the 2 g metronidazole regimen is included in the treatment guideline provided by the Australian Sexual Health Alliance.[14]

A novel vaginal suppository containing metronidazole 750 mg plus miconazole nitrate 200 mg (Neo-penotrans Forte®; NPF, Exeltis, Thailand) may be an alternative treatment modality. Previous studies showed that an oral metronidazole tablet can be used intravaginally for treating women with BV.[10-11] The novel vaginal suppository, which dissolves more readily, had been reported to have high efficacy against BV, trichomoniasis and fungal infection: 75-96%, 100%, and 82-90%, respectively.[15,16] Also, NPF can effectively cure mixed infection.[15,16] A monthly 7-day course of NPF for up to 3-8 months was found to prolong remission period among women with recurrent BV.[17] Another benefit of this vaginal suppository is that there have never been any serious adverse events reported.[16,18] However, with different backgrounds of the users, the efficacy is yet to be validated in Thai women. The present study aims to compare the cure rate and symptomatic recurrence rate between a 7 day-course of vaginal metronidazole 750 mg plus miconazole nitrate 200 mg NPF and a single oral dose of 2 g oral metronidazole in treating BV. Side effects of treatment and the women's satisfaction were also evaluated.

MATERIALS AND METHODS

This prospective open-labelled randomized clinical trial was carried out at the Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, during September 2019 – March 2020. The ethical approval was obtained from the Siriraj Institutional Review Board (Si 222/2019). The trial was registered at the Thai Clinical Trials Registry (TCTR20200902002).

Participants

All women who aged 18-45 years and were diagnosed with BV by Amsel's criteria were invited to participate in the study. The diagnosis based on Amsel's criteria required at least 3 of the following criteria: thin white/grey homogenous discharge, pH>4.5, fishy (amine) odor and the presence of clue cells.[19] The exclusion criteria were women who: had a history of allergy to metronidazole or miconazole, were immunocompromised, had previous episodes of BV within 3 months, had taken medications that could disrupt the vaginal ecosystem e.g. anti-parasitic drugs, oral antibiotics, any vaginal medications, anti-coagulant, or disulfiram within the previous month, had co-incidental STIs or cervical pre-cancerous or cancerous lesions, was currently pregnant or lactating, or had abnormal uterine bleeding.

Intervention

All women who presented with abnormal vaginal discharge at the Siriraj Female Clinic were informed about the study before entering examination rooms. Then, they underwent history-taking, pelvic examination and wet preparation. The initial evaluation using a microscope took around 5 minutes for diagnosing BV based on Amsel's criteria. The eligible participants were explained in detail about the study by a study nurse and signed the informed consent. After that, another high vaginal swab was collected for gram stain and Nugent's scoring system. Demographic data, as well as pre-treatment symptom evaluation, were then collected by the study nurse.

The randomization was computer-generated using block-of-four with a ratio 1:1. Each participant was allocated to receive either a 7-day course of vaginal suppository containing metronidazole 750 mg plus miconazole nitrate 200 mg (Neo-penotrans Forte®; NPF, Exeltis, Thailand) or a single dose of oral 2gm metronidazole (Metrolex®, Siam Bheasach Co., Ltd., Thailand).

The participants who were assigned to use vaginal suppository were trained to perform a proper self-insertion of vaginal suppository using a manikin. The single oral dose of metronidazole was given 45 minutes following the oral consumption of domperidone 10 mg at the Clinic on the recruitment day. All participants

were asked to comply with the following prohibitions: no sexual activity, no vaginal douching or cleansing, and avoiding alcoholic beverages for one week following treatment.

All participants were scheduled for a 2-week follow up visit. Clinical response, wet preparation and gram stain for Nugent scoring were done by an investigator (Chayachinda C). Satisfaction and side effects were evaluated by a study nurse. Those who had persistent BV were treated with metronidazole 400 mg per oral thrice a day for 7 days; or who had other diagnosis were treated accordingly. At 1-month and 3-month post-treatment, all participants were telephoned asking about symptomatic recurrence and/or additional treatment.

Outcome measures

At 2-week follow-up, outcome measures were clinical response, cure rate by Amsel's criteria, cure rate by Nugent's scoring, satisfaction and side effects. Five key symptoms which were evaluated by a study nurse including vaginal discharge, irritation, itching, odor and coital pain, were graded into 0 (no/absent), 1 (mild), 2 (moderate) and 3 (severe). This results in the ranging score from 0-15. At least 75% reduction of the scores was defined as 'clinical response'. Satisfaction and side effects were also evaluated by the study nurse; and being reported using 0-10 from 'no' to 'maximum'.

The diagnosis of BV based on Amsel's criteria required at least 3 of the following criteria: thin white/grey homogenous discharge, pH > 4.5, fishy (amine) odor and the presence of clue cells.[19] The Nugent scoring was assessed by a blinded microbiologist. The gram-stained slides, two for each participant (first visit and follow-up visit), were labeled using code numbers; and were sent to the microbiologist all at once. The scoring system was done by looking for *Lactobacillus spp., Gardnerella/Bacteroides spp.*, and curved gram variable rods. The scores ranged from 0-10 and are categorized into 3 groups: score 0-3 (normal), score 4-6 (intermediate flora) and score 7-10 (BV).[20] Cure rate was defined as the conversion of BV to non-BV, including reduction of Amsel's criteria from ≥3 to <3 criteria or that of Nugent score from ≥7 to <7.

At 1-month and 3-month post-treatment, the telephone interview regarding current symptoms, symptomatic recurrence and additional treatment was done by a study nurse who was blinded to the allocation.

Sample size calculation and statistical analysis

Data analyses were carried out with STATA version 12.1 (Stata Corp LP, College Station, Texas, USA). To describe the characteristics of the participants, mean ± standard deviation, n (%), and median with range were used. For categorical variables, comparison was performed using the chi-squared test or Fisher's exact test. The distribution of each continuous variable was tested using the Shapiro–Wilk test. Parametric continuous variables were compared with Student's t-test, while nonparametric continuous variables were analyzed with the Wilcoxon rank-sum test. Univariate and multivariate logistic regression were used to determine treatment efficacy. A *P*-value of < 0.05 was deemed statistically significant.

The sample size calculation was undertaken using a formula that compared 2 proportions. A study by Chaithongwongwatthana et al. showed that the efficacy of a single dose of 2 g metronidazole to for BV treatment was 78.6%[12], whereas another study by Regidor showed that the cure rate in women using NPF was 98.1%.[16] The required sample size was determined to be 30 per group (power, 70%; alpha, 0.05). As a loss-to-follow-up rate of 30% was expected, 40 participants needed to be recruited to each group.

RESULTS

Of 84 eligible participants, 70 came for the two-week follow-up and were included in the analysis. (NPF N=34, MET N=36) Sixty-nine and 60 were contacted at one-month and three-month respectively (Fig 1). The average age and body mass index (BMI) were 32.3±7.9 years and 21.6±3.8 kg/m^2. Around half of all participants reported regular external vaginal cleansing after urination and 8.6% reported ever vaginal douching. Ten participants reported history of sexually transmitted diseases (STD), including 5 genital warts, 3 genital herpes and 2 PID. (Table 1)

All treatment outcomes at two weeks are shown in Table 2. After adjusting for age, sexual experience and number of lifetime sex partners, both NPF and MET had comparable efficacy. Improvement of each symptom was demonstrated in Table 3. Table 4 shows clinical score, Amsel's criteria and Nugent's scores before the intervention and 2-week post treatment. There was no difference between NPF and MET except that the total Nugent's score in NPF group was significantly lower at 2-week follow-up (5.4±1.9 vs 6.8±1.9, p=0.004). At the two-week follow-up, four participants were diagnosed with vaginal candidiasis (NPF 1/34, 2.9% vs MET 3/36, 8.3%, p=0.331); and none had BV.

Both groups reported high satisfaction (NPF 8.5±1.4 vs MET 7.9±2.0, p=0.125). No drug allergy was

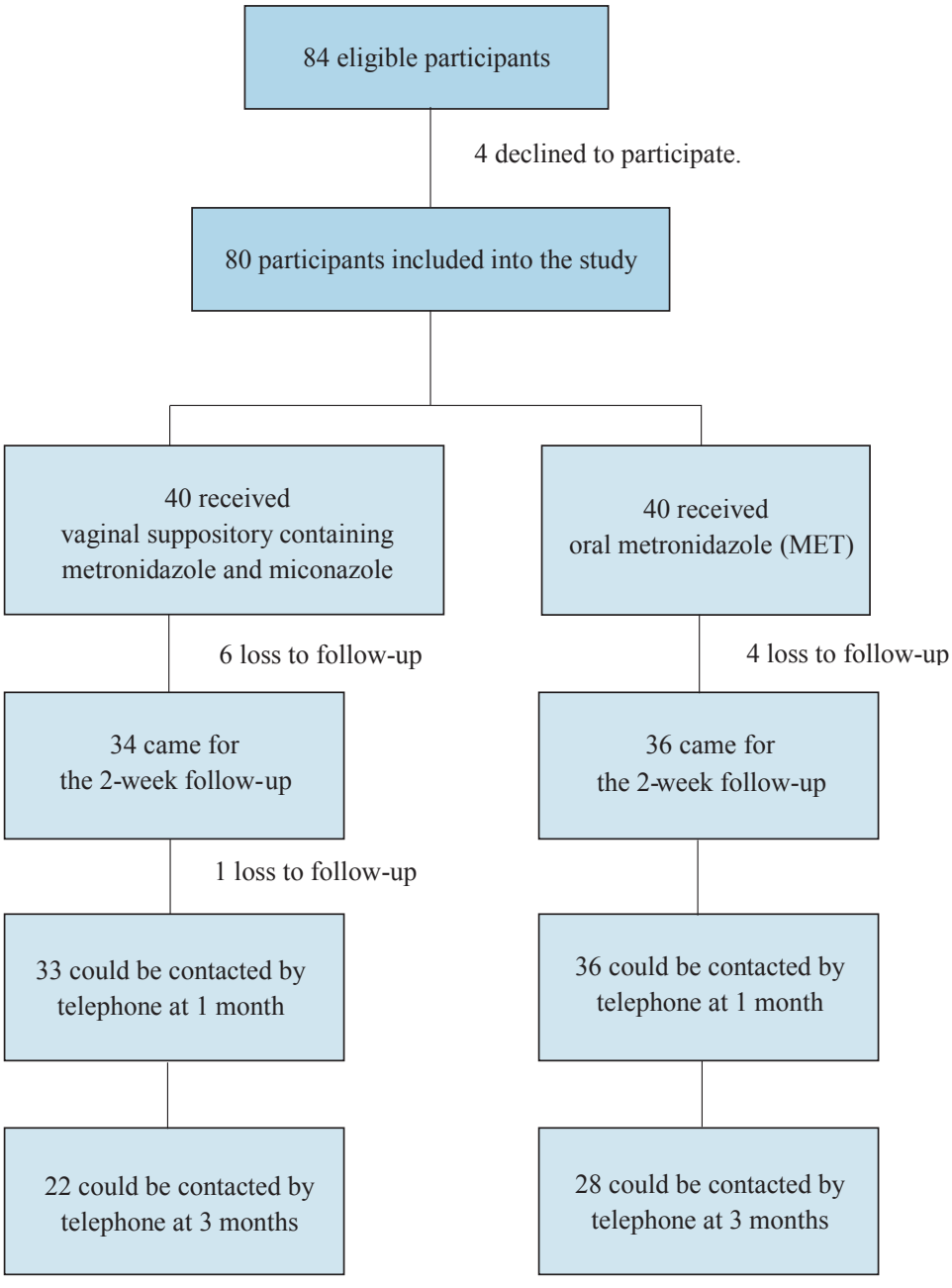

Fig 1. Flow of the participants.

reported but the side effects were as the followings: loss of appetite/metallic taste (NPF 5/34, 14.7% vs MET 6/36, 16.7%, p=0.822), nausea (NPF 3/34, 8.8% vs MET 6/36, 16.7%, p=0.327), dizziness (NPF 4/34, 11.8% vs MET 5/36, 13.9%, p=0.791), vaginal irritation (NPF 3/34, 8.8% vs MET 6/36, 16.7%, p=0.327) and pelvic pain/diarrhea (NPF 2/34, 5.9% vs MET 1/36, 2.8%, p=0.522). No symptomatic, recurrent episode of BV was reported at one-month and three-month telephone follow-ups.

DISCUSSION

Both vaginal suppository containing metronidazole (750 mg) and miconazole nitrate (200 mg) and a single dose of oral metronidazole (2 g) for BV treatment demonstrate comparable clinical cure and laboratory-based cure rate. The high efficacy demonstrated by NPF in the present study was consistent with a meta-analysis done by Lugo-Miro VI et al.[10] Our findings support the potential of this medication as a first-line treatment for BV. Given that oral metronidazole has remarkable side effects of gastrointestinal irritation when BV is localized dysbiosis of the vaginal ecosystem, topical treatment modality appears promising. Moreover, a vaginal biofilm of *G. vaginalis* may limit the treatment efficacy of oral metronidazole.[21]

TABLE 1. Characteristics of the participants (N=70).

	Total (N=70)	NPF (N=34)	MET (N=36)
Age (years)	32.3±7.9	34.1±8.1	30.6±7.3
<25	15 (21.4)	4 (11.8)	11 (30.6)
25-35	32 (45.7)	16 (47.1)	16 (44.4)
>35	23 (32.9)	14 (41.2)	9 (25.0)
Body mass index (kg/m^2)	21.6±3.8	21.5±3.7	21.7±3.8
<18	10 (14.3)	6 (17.7)	4 (11.1)
18- <25	47 (67.1)	21 (61.8)	26 (72.2)
≥25	13 (18.6)	7 (20.6)	6 (16.7)
Being a mother	31 (44.3)	15 (44.1)	16 (44.4)
Abortion	13 (18.6)	5 (14.7)	8 (22.2)
Contraception			
No	23 (32.9)	15 (44.1)	8 (22.2)
Condom	16 (22.9)	4 (11.8)	12 (33.3)
Oral contraceptive pill	21 (30.0)	9 (26.5)	12 (33.3)
Implant/ injectable contraception	4 (5.7)	3 (8.8)	1 (2.8)
No sexual experience	14 (20.0)	10 (29.4)	4 (11.1)
Number of lifetime sex partners	2 (0-4)	1 (0-4)	2 (0-4)
Vaginal hygiene			
Excessive Cleansing	37 (52.9)	17 (50.0)	20 (55.6)
Douching	6 (8.6)	3 (8.8)	3 (8.3)
History of sexually transmitted diseases	10 (14.3)	3 (8.8)	7 (19.4)

*Wilcoxon Ranksum test

Abbreviations: NPF = neo-penotran forte, MET = metronidazole

TABLE 2. Treatment outcomes (N=70).

	Total	NPF	MET	P	cOR (95% CI)	aOR* (95% CI)
Clinical cure rate	44/70 (62.9)	23/34 (67.7)	21/36 (58.3)	0.420	1.49 (0.56-3.97)	1.35 (0.46-3.99)
Cure rate based on Amsel's criteria	56/70 (80.0)	28/34 (82.4)	28/36 (77.8)	0.632	1.33 (0.41-3.43)	5.79 (0.88-37.99)
Cure rate based on Nugent scores	18/70 (25.7)	12/34 (35.3)	6/36 (16.9)	0.075	2.73 (0.89-8.39)	2.73 (0.83-8.96)

*adjusting for age, sexual experience, number of lifetime sex partners

Abbreviations: NPF = Neo-penotran forte®, MET = metronidazole, cOR = crude odd ratio, aOR = adjusted odd ratio

TABLE 3. Comparison of symptoms at each visit.

	Before treatment (N=70)			2 weeks (N=70)			1 month (N=69)			3 months (N=60)		
	NPF (n=34)	MET (n=36)	P	NPF (n=34)	MET (n=36)	P	NPF (n=33)	MET (n=36)	P	NPF (n=22)	MET (n=28)	P
Vaginal discharge												
0	0	0	0.252	14 (41.2)	11 (30.6)	0.214	12 (36.4)	10 (27.7)	0.683	7 (31.8)	10 (35.7)	0.870
1	9 (26.5)	6 (16.7)		18 (52.9)	18 (50.0)		16 (48.5)	20 (55.6)		11 (50.0)	14 (50.0)	
2	15 (44.1)	23 (63.9)		2 (5.9)	7 (19.4)		5 (15.1)	5 (13.9)		2 (9.1)	3 (10.7)	
3	10 (29.4)	7 (19.4)		0	0		0	1 (2.8)		2 (9.1)	1 (3.6)	
Vaginal irritation												
0	1 (2.9)	0	0.397	27 (79.4)	22 (61.1)	0.114	25 (75.7)	29 (80.5)	0.964	17 (77.2)	22 (78.6)	0.248
1	7 (20.6)	8 (22.3)		7 (20.6)	11 (30.6)		5 (15.2)	4 (11.1)		4 (18.2)	3 (10.7)	
2	10 (29.4)	16 (44.4)		0	3 (8.3)		2 (6.1)	2 (5.5)		0	3 (10.7)	
3	16 (47.1)	12 (33.3)		0	0		1 (3.0)	1 (2.8)		1 (4.6)	0	
Vaginal itching												
0	8 (23.5)	8 (22.2)	0.962	26 (76.5)	24 (66.7)	0.325	28 (84.9)	29 (80.6)	0.613	17 (77.3)	22 (78.6)	0.627
1	10 (29.4)	11 (30.6)		8 (23.5)	10 (27.8)		5 (15.2)	6 (16.7)		5 (22.7)	5 (17.9)	
2	12 (35.3)	14 (38.9)		0	2 (5.6)		0	0		0	1 (3.5)	
3	4 (11.8)	3 (8.3)		0	0		0	1 (2.7)		0	0	
Malodorous discharge												
0	22 (64.7)	17 (47.2)	0.311	29 (85.3)	32 (88.8)	0.579	33 (100)	33 (91.7)	0.238	21 (95.5)	26 (92.8)	0.662
1	7 (20.6)	8 (22.2)		4 (11.8)	2 (5.6)		0	2 (5.5)		1 (4.5)	1 (3.6)	
2	2 (5.9)	7 (19.4)		1 (2.9)	2 (5.6)		0	1 (2.7)		0	1 (3.6)	
3	3 (8.8)	4 (11.2)		0	0		0	0		0	0	
Coital pain												
0	4 (11.8)	6 (16.7)	0.651	30 (88.2)	32 (88.9)	0.562	31 (93.9)	31 (86.1)	0.238	20 (90.9)	26 (92.8)	0.249
1	12 (35.2)	14 (38.9)		4 (11.8)	3 (8.3)		0	3 (8.3)		2 (9.1)	0	
2	7 (20.6)	9 (25.0)		0	1 (2.8)		2 (6.1)	2 (5.6)		0	1 (3.6)	
3	11 (32.4)	7 (19.4)		0	0		0	0		0	1 (3.6)	
Total score	8(1-12)	8(3-11)	0.795	1(0-5)	2(0-8)	0.218	1(0-6)	1(0-9)	0.852	2(0-7)	1(0-8)	0.263

Abbreviations: NPF = Neo-penotran forte®, MET = metronidazole

TABLE 4. Clinical score, Amsel's criteria and Nugent's score before the intervention and at 2-week follow-up (N=70).

	Before the intervention			2-week follow-up		
	NPF (n=34)	MET (n=36)	P	NPF (n=34)	MET (n=36)	P
Sum of clinical scores	8(1-12)	8(3-11)	0.795	1(0-5)	2(0-8)	0.218
Amsel's criteria						
Homogeneous whitish discharge	17 (50.0)	22 (61.1)	0.350	11 (32.4)	11 (30.6)	0.871
pH >4.5	34 (100)	36 (100)	1.000	7 (20.6)	15 (41.7)	0.058
Positive whiff test	29 (85.3)	34 (94.4)	0.202	6 (17.7)	8 (22.2)	0.632
Presence of clue cells	34 (100)	35 (97.2)	0.328	7 (20.6)	11 (30.6)	0.340
Total	3 (3-4)	3 (3-4)	0.342	1 (0-3)	1 (0-3)	0.902
Nugent's score						
Normal (score <4)	0	0	0.653	8 (23.5)	4 (11.1)	0.032
Intermediate flora (4-6)	5 (14.7)	4 (11.1)		12 (35.3)	6 (16.7)	
Bacterial vaginosis (>6)	29 (85.3)	32 (88.9)		14 (41.2)	26 (72.2)	
Total score	7.6±1.0	7.8±0.9	0.291	5.4±1.9	6.8±1.9	0.004

Abbreviations: NPF = Neo-penotran forte®, MET = metronidazole,

Amsel's criteria at two-week follow-up were not different whereas Nugent's scores were. Amsel's criteria partially belonged to clinical-based diagnostic methods when Nugent's scoring system was mainly a laboratory-based method. The latter one was usually used as a gold-standard diagnostic method in research study. Obviously, Nugent's scoring system had a better reflection of vaginal ecosystem as our previous study showed that, based on this method, 20% of asymptomatic pregnant women had BV; and tended to have worse pregnancy outcomes.[22] Therefore, the higher cure rate based on Nugent's scoring system in the present study suggested the better recovery of vaginal dysbiosis following NPF treatment.

Contrasting to previous studies, none of the participants in the present study reported symptomatic recurrence. A longer course of metronidazole results in a lower incidence of recurrence at 1 month.[10] Moreover, a long-term study in Australian women found that over 50% of BV-diagnosed women receiving or not receiving adjuvant treatment reported recurrent BV episodes at their 6-month follow-up.[23] This may be partly explained by the fact that practice to achieve and maintain vaginal hygiene were emphasized during participant counselling, such as avoiding excessive cleansing, vaginal douching, and the wearing of tight garments.

Compatible with previous studies, the combination of metronidazole and miconazole in a vaginal suppository appear not to cause more severe adverse events; but mitigate the coincidence of BV and vaginal candidiasis (VC).[15,16] The coincidence was reported in 15.2% of American non-pregnant women[16] and 13.3% of Thai pregnant women.[22] Furthermore, the administration of miconazole (200 mg) vaginal suppositories for 3 days is a recommended regimen for treating women with VC treatment guidelines.[9,23] The present study shows that pseudohyphae was detected around three times higher in the MET group at 2-week.

Although none of the participants required additional BV treatment within 3 months post-treatment, a quarter of the participants reported a malodorous vaginal discharge or fishy odor following sexual intercourse. This supports the dynamic and self-heal of vaginal microbiome. Despite the fact that seminal fluid can enhance the symptom of BV, the resumption of individual participant's normal life is the goal of BV treatment. As such, other risk factors of BV occurrence should be serious taken into consideration such as excessive vulvar cleansing and vaginal douching.

The strength of this study is the randomized design. Although the participants could not be blinded, the

investigators who evaluated the outcome measures and the statistician were. The limitations of the study included its small sample size and short follow-up period. Only symptomatic recurrence is approached at 1- and 3-month while BV can be asymptomatic and frequently recurs at 6 months post treatment. Another limitation is that the administrative route and the duration of treatment period of the two assigned treatment are different. Provided that double-dummy, placebo-controlled design and daily self-record of symptoms had been applied, the study might have had less reporting biases.

In conclusion, for BV treatment, both vaginal suppository containing metronidazole (750 mg) plus miconazole nitrate (200 mg) and oral metronidazole (2 g) show comparable efficacy and side effects.

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