International Journal of Pharmacological Research www.ssjournals.com
ISSN: 2277-3312 Journal DOI:10.7439/ijpr

Efficacy and safety of oral tinidazole and metronidazole in treatment of bacterial vaginosis: a randomized control trial

Zahra Abbaspoor[1], Zeinab Rabee[2] and Shahnaz Najjar[2]

[1]*Ph.D of Reproductive Health, Faculty of Nursing and Midwifery, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
[2]*Msc in Midwifery, faculty of Nursing and Midwifery, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

Corresponding author*:
Zahra Abbaspoor,
PhD of Reproductive Health,
Department of Midwifery, Faculty of Nursing and Midwifery,
Ahvaz Jundishapur University of Medical Sciences, Golestan Blvd. Ahvaz, Iran, 61357-33184.
E-mail: Abbaspoor_z762@yahoo.com

Abstract
Aims: Oral metronidazole 500 mg twice a day for one week is currently the treatment of choice for bacterial vaginosis (BV). Complete treatment by this regimen takes time and occurs less often. This drug has significant side effects too. Using a drug in the shortest treatment course may increases the success of treatment. To evaluate the effectiveness and safety of oral tinidazole compare to metronidazole in treatment of BV.
Methods: In this randomized, controlled, double-blind, comparative, clinical trial, 110 non-pregnant women aged between 15-45 years with confirmed diagnosis of BV by Amsels criteria were randomly assigned to receive either 2 g tinidazole tablet once daily for 2 days (n=55) or 500 mg metronidazole table twice daily for 7 days (n=55).The cure and recurrence rate were evaluated in both groups after 2 and 4 weeks follow up visits. For statistical analysis t-test, x^2 test, fisher's exact test and Mann-Whitney test were used.
Results: The results showed that cure rate after 2 weeks in tinidazole tablet group was 84.6٪ and in metronidazole group was 85.4٪ (p=0.9), and after 4 weeks recurrence rate in tinidazole and metronidazole groups was 6.9٪and 12.1٪respectively (P=0.3).
Conclusions: Tinidazole table 2 g once daily for 2 days is as effective as metronidazole tablet 500 mg twice a day for 7 days in treatment of BV.
Keywords: Bacterial vaginosis, metronidazole, tinidazole

1. Introduction
Vaginitis is the most common gynecological problems that women seek for its treatment.[1] Vaginitis is detected by some signs and symptoms include: increased external dysuria, vulvular irritation and itching, vaginal discharge, odor, or yellow discharge. These symptoms are not significant markers to detect the specific cause of vaginitis.[2] BV is the most common cause of abnormal discharge in women in reproductive age,[3,4] it may also be encountered in postmenopausal women and children rarely.[5] It defines as a change in the normal vaginal bacterial flora in which the normal lactobacilli-producing hydrogen peroxide replaces by an overgrowth of anaerobic bacteria with a predominant species such as gardenela vaginalis, protela species, bactrioid species, mobiluncus species, gram-positive cocci and Mycoplasma.[3,6,7] The prevalence of BV in America is 29.2% and it is a reason for ten million clinical visits annually for vaginitis. As a whole, prevalence varies from 5% to 60% of women treated at STDs clinics. In pregnancy based on diagnostic methods this prevalence ranged from 12% to 55 %.[8] In Iran prevalence of BV (2002) was 27% in Sanandaj city and in 2005 was 37.7% in Kerman city.[7,9]

BV has been associated with an increased rate of serious obstetrical and gynecological complications include postpartum endometritis after delivery, caesarean section or abortion, increased rate of infection after hysterectomy, vaginal cuff cellulitis after abdominal hysterectomy, wound infection following caesarean section, pelvic inflammatory disease after therapeutic abortion, premature rupture of fetal membranes, preterm labour, chorioamnionitis, spontaneous abortion, recurrent urinary tract infection and increased rate of cervical intraepithelial neoplasia.[5] In Martin study(1999) HIV seroconversion was associated with BV[10]. Patients with BV have an increased rate at STDs and 2 to 4 times increases in HIV transmission.[3,4,11]

Although Choice treatment for bacterial vaginosis is currently metronidazole 500 mg b.i.d for 7 days, with a 80-90% cure rate,[12] but 50–70% women after treatment will have a recurrence in 4-6 weeks, 70% will have a recurrence rate within next 90 days and another episode of BV within a year in 80% of women.[13] In addition the use of systemic metronidazole is the potential for several adverse effects during therapy, including heartburn, metallic taste in the mouth and skin rash.[14] Other complications include seizures, neuropathy, headache, vomiting, and diarrhea and May leucopenia.

some patients taking metronidazole can show or may suffering from candida vaginitis.[14,15]

Also the seven-day regimen of metronidazole takes a long time and taking entire course therapy due to forgetting some dosage may lead to incomplete treatment and finally eradication of the organism occur less often.[16] Therefore, a shorter duration treatment regime with fewer adverse effects and recurrent rate but with the same cure rate for BV has been preferred. This issue prompted researches to do study for alternative therapies. Tinidazole has suggested as an effective alternative drug for the treatment of bacterial vaginosis. Tinidazole is derived from the Nitroimidazole class and it is an anti-protozoa drug. First time in 1967, it introduced to clinical medicine for the treatment of trichomonas vaginalis infection. After that, it was used for treatment of protozoa infections such as giardiasis, amibiasis, Helicobacter pylori and anaerobic infections like intraperitoneal infection, postoperative wound infections, skin and soft tissue infections and bacterial vaginosis.[17] As reported by John *et al*(2011) there was no difference between treatment with metronidazole and tinidazole in different dozage and their adverse effects.[18] Also, Tolcar *et al* (2012) in their study reported that in the treatment of bacterial vaginosis, tinidazole was more effective than metronidazole.[19] Tinidazole compared to metronidazole had a longer half-life (2 times), and fewer side effects especially metallic taste in mouth and gastrointestinal problems. Tinidazole also is cheaper than metronidazole.[17,20] Therefore, this study designed on comparing effect of oral tinidazole 2 g once daily for 2 days with oral metronidazole, 7 days in treatment and recurrence rate of BV among Iranian women.

2. Materials and Methods

The present study was designed as randomized, double-blind, controlled two–groups comparative study conducted on 110 married, non-pregnant women aged 15-45 years old, were proved for BV in governmental hospital and Quds clinic, Kangan city, Iran, 2012.

Criteria for diagnosis BV were presence of three of the four standard diagnostic of Amsel criteria were include: 1) homogeneous vaginal discharge 2) to positive whiff test 3) clue cells> 20 % in the vaginal wet smear and 4) vaginal pH ≥4.5. After a pelvic examination, at baseline, the vaginal secretion collected from the lateral vaginal walls cultured and evaluated for whiff test, gram stain and pH measurement.

Exclusion criteria were include chronic diseases (diabetes, cardiovascular disease, etc.), no history of hypersensitivity to metronidazole and its derivatives, the use of metronidazole and other antibiotics within past 2 weeks, treatment with immunosuppressive drugs.

Eligible patients based on attendance coding were randomly assigned and divided to two treatment groups. One group (n=55) received 2 g oral tinidazole at bedtime for 2 days and the second group (n=55) received 500 mg oral metronidazole twice daily at bedtime for seven days. For blindness, another midwife was asked to provide the drugs in two the same packages and named them (A or B). In addition, she was asked to give the A package to first eligible patient and B package to the next eligible patient and explain how to use them.

Patients were prohibited for vaginal washing, intercourse and using any vaginal drug during the course treatment. Treatment was defined as the presence of less than three Amsel criteria. Measurements were repeated on the 2th week (visit 2) (Fig 1).

Figure 1. Requirement and participation of patients

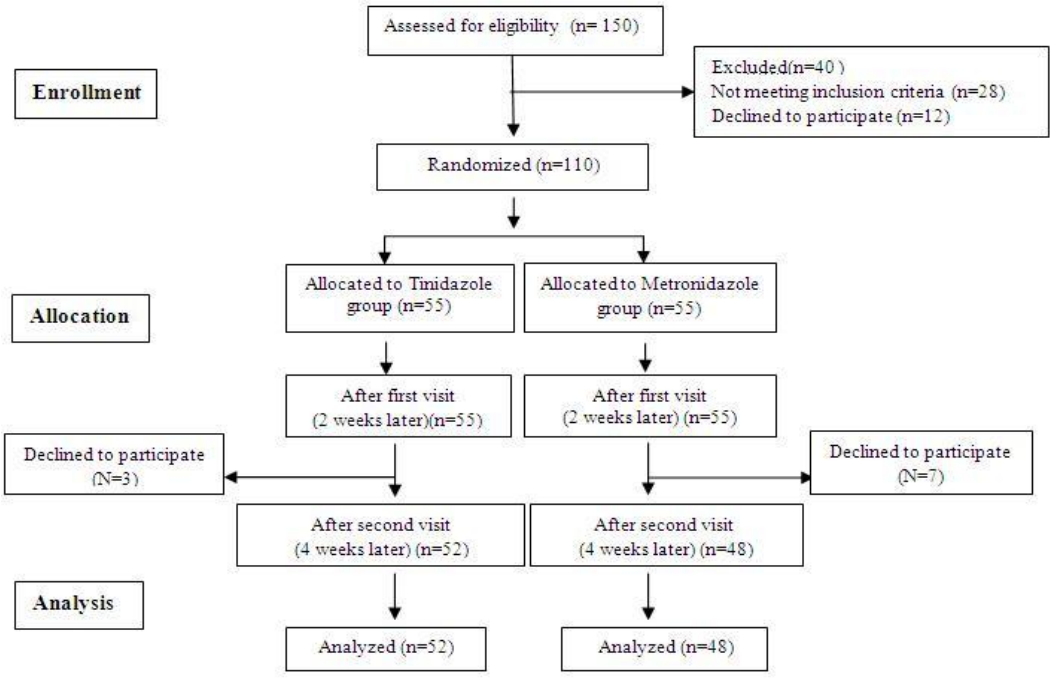

Figure Legend: Eleven patients discontinued the study: 2 in tinidazole group (because of failure to follow- up) and 7 in metronidazole group (because of not consuming the drugs fully).

Patients who had not cured in this stage were referred to a gynecologist for treatment and the rest (44 patients in tinidazole group and 41 patients in metronidazole group) were evaluated 4 weeks after treatment for recurrence (visit 3). Symptoms of BV, adverse effects and treatment compliance were recorded. Before starting the sampling, written informed consent was obtained from each patient.

2.1 Laboratory tests

Three smears were made from the vaginal discharge. Upon the first slide, a small amount of 10% potassium hydroxide (KOH) was dripped and a rotten fishy odor was recorded as positive, then the smear examined for Candida Albicans especially as Hiff form, microscopically.

In addition, some vaginal discharge was scraped off to a pH paper (Merck brand, Germany, with 0.5 sensitivity) and was compared to the standard. Some Vaginal discharge mixed with 2 drops of normal saline for microscopic examination. Clue cells and mobile trichomonas vaginalis were searched in the vaginal smear. Two smears made from vaginal discharge and gram stained. One smear was read by the research assistant at the study site. The second smear was read by a pathologist for the presence of clue cells and permanent trichomonas vaginalis.

2.2 Statistical methods

The statistical analysis was carried out by SPSS version 16. Statistical analysis was performed using independent *t* test and chi-square test to compare patients' baseline characteristics and analyze the difference in the proportion of patients with positive whiff test and clue cells across treatment groups. Mann-Whitney and Fisher exact test also was used to compare cure and recurrent rate in treatment groups.

Some data were expressed as mean ± SD; the significance level was set up at p less than 0.05.

2.3 Ethical considerations

This randomized controlled study was approved by the Research Ethics Committee of Ahvaz Jundishpur University of Medical sciences and registered with the Iranian clinical trials (http://irct.ir). Women completed informed written consent form. To ensuring data set anonymity each woman was assigned an ID code.

3. Results

The treatment groups compared for some demographic and clinical reproductive characteristics at baseline and differences were not statistically significant (p > 0.05)(Table 1).

Table 1. Demographic and clinical characteristics at baseline by treatment groups.

Group	Tinidazole	Metronidazole	p value
Age, y, mean(SD)	31.2±7.1	30.6±7.3	0.6
Marriage age, y mean(SD)	20.7±4.4	19.9±3.7	0.3
Parity, n (%>1 children)	46(81.2%)	39(88.5%)	0.5
Previous preterm labour, n(%)	3(6.6%)	4(10%)	0.5
Relation with intercourse n(%)	38(73.1%)	36(75%)	0.8
Previous vaginitis n(%)	18(34.6%)	15(31.3%)	0.7

χ^2 test, P>0.05; not significant. *t*- test P>0.05; not significant. Fisher's exact test P>0.05; not significant.

3.1 Homogenous vaginal discharge

The most common complaint of patients in both groups was a foul-smelling vaginal discharge (80.8% in Tinidazole group, and 72.9% in the metronidazole group). The second common complaint of patients was a massive vaginal discharge (19.2% in tinidazole group and 27.1% in metronidazole group). The results showed that homogenous vaginal discharge was not significantly different across treatment groups 2 and 4 weeks after treatment (p =0.7, p =0. 6, respectively), but in follow-up visits there was a trend of lower incidence in homogenous vaginal discharge (Table 2).

Table 2. Frequency and percent of homogenous discharge at each clinic visit by treatment groups.

	Baseline		2 weeks after treatment		4 weeks after treatment	
Groups	Tinidazole	Metronidazole	Tinidazole	Metronidazole	Tinidazole	Metronidazole
Homogenous discharge	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**
Present	52 (100)	48 (100)	10 (19.2)	8 (16.7)	6 (13.64)	7 (17)
Absent	0 (0)	0(0)	42 (80.8)	40 (83.3)	38 (86.36)	34 (83)
Total	52 (100)	48 (100)	52 (100)	48 (100)	44 (100)	41 (100)
p value	0.999		0.7		0.6	

χ2 test, P>0.05; not significant

3.2 Whiff test

There was not significant different in positive whiff tests across treatment groups (p=0.8, p=0.7 respectively, and at follow-up visits; Table 3).

Table 3: Frequency and percent of whiff test results at each clinic visit by treatment groups.

	Baseline		2 weeks after treatment		4 weeks after treatment	
Group	Tinidazole	metronidazole	Tinidazole	metronidazole	metronidazole	Tinidazole
Whiff test	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**
Positive	51(98.1)	48(100)	8 (15.4)	8(16.7)	4(9.1)	3(7.32)
Negative	1(1.9)	0(0)	44 (84.6)	40(83.3)	40(90.9)	38(92.68)
Total	52(100)	48(100)	52(100)	48(100)	44(100)	41(100)
p value	0.3		0.8		0.7	

$\chi 2$ test, P>0.05; not significant. Fisher's exact test P>0.05; not significant.

3.3 Change in pH level

Table 4 presents descending pH levels through time but such changes were not significantly different across tinidazole and metronidazole groups (p =0.3, p=0.6, respectively).

Table 4. Frequency and percent of vaginal acidity rate at each clinic visit by treatment groups

	Baseline		2 weeks after treatment		4 weeks after treatment	
Group	Tinidazole	metronidazole	Tinidazole	metronidazole	Tinidazole	metronidazole
pH	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**
≥ 4.5	52 (100)	48 (100)	11 (21.2)	14 (29.2)	10 (22.73)	11 (26.83)
< 4.5	0 (0)	0 (0)	41 (78.8)	34 (70.8)	34 (77.27)	30 (73.17)
Total	52 (100)	48 (100)	52 (100)	48 (100)	44 (100)	41 (100)
p value	0.999		0.3		0.6	

$\chi 2$ test, P>0.05; not significant.

3.4 Clue cells

The tinidazole and metronidazole tablets had similar effects on the percent of clue cells 2 and 4 weeks after treatment and there was not statistically significant difference across treatment groups (p = 0.8, p = 0.5) respectively (Table 5).

Table 5. Frequency and percent of Clue cell at each clinic visit by treatment groups

	Baseline		2 weeks after treatment		4 weeks after treatment	
Group	Tinidazole	metronidazole	Tinidazole	metronidazole	Tinidazole	metronidazole
Clue cell> 20%	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**
Yes	49(94.2)	46(95.8)	5(9.6)	4(8.3)	3(6.82)	3(7.32)
No	3(5.8)	2(4.2)	47(90.4)	44 (91.7)	41 (93.18)	38 (92.68)
Total	52(100)	48(100)	52(100)	48(100)	44(100)	41(100)
p value	0.7		0.8		0.5	

Fisher's exact test P>0.05; not significant

3.5 Cure and recurrence rates

Table 6 presents the observed cure and recurrence rates in two treatment groups. Two weeks after treatment the cure rate in the tinidazole group was 84.6%, and in the metronidazole group was 85.4% but, there was no significant difference across treatment groups (p = 0.9). Fore weeks after treatment recurrence rate in tinidazole group was 6.9% and in metronidazole group was 12.1%, but also this difference was not significant (p = 0.3)(Table 6). Also, the first day that patients felt a cure feeling in their symptoms after starting the treatment in tinidazole group was 4.4 day and in metronidazole group was 7.3 day. The Mann-Whitney test showed a significant difference between the two groups (p =0.0001) and tinidazole tablet was able to make an earlier cure feeling than metronidazole tablet.

Table 6. Frequency of cure and recurrent vaginal discharge at 4 weeks after treatment by treatment groups

Group		Tinidazole	Methronidazole	P value
		Freq (%)	**Freq (%)**	
Cure	Yes	44(84.6)	41(85.4)	0.9
	No	8(15.4)	7(14.6)	
Recurrent	Yes	3(6.9)	5(12.1)	0.3
	No	41(93.1)	36(87.9)	

$\chi 2$ test, P>0.05; not significant. Fisher's exact test P>0.05; not significant

3.6 Tolerability and safety

Adverse events were fewer in tinidazole group (5.8%) versus (20.8%) in metronidazole group. This difference was statistically significant (p= 0.025). These adverse events in tinidazole group were include: drowsiness (one case), and metallic taste in the mouth (two cases) and in metronidazole group were include dark urine, metallic taste in the mouth and drowsiness.

4. Discussion

Bacterial vaginosis is a change in the normal vaginal bacterial flora by increased homogenous vaginal discharge, low viscosity and smoothly coats the vaginal mucosa.[21] The primary mechanism in controlling the composition of the microflora has known as low vaginal pH(3.8-4.2) among reproductive age women.[22,23] Lactobacilli can inhibit the growth of pathogenic organisms such as BV and metronidazole is a gold standard drug in treatment of BV with a potent antimicrobial activity against anaerobes that can inhibit lactobacilli. Sometimes due to long duration of treatment with metronidazole, patients couldn't complete the treatment days.[15] In this study oral tinidazole(2 g oral tinidazole at bedtime for 2 days) and metronidazole (oral metronidazole 500 mg twice daily at bedtime for 7 days) (as usual treatment) for treatment of BV were utilized.

Based on the results, tinidazole and metronidazole in treatment of BV have a similar impact, so 2 weeks after treatment 84.6% of patients in the tinidazole group and 85.4% of patients in the metronidazole group were cured. In study performed by Mohan *et al.*[20] cure rate in tinidazole group(2 g single dose) was 92% and in the metronidazole group (2 mg single dose) was 79% that is comparable to present study. Furthermore, in a study performed by John *et al.*[16] Two weeks after treatment cure rate in metronidazole tablet group was 80.3%, in tinidazole tablet group (1 gram) was 82.5% and in tinidazole tablet group (500 mg) was 73.1%. In our study 4 weeks after treatment there was a low recurrence rate in treatment groups, 6.9% and 12.1% in the tinidazole and metronidazole group respectively, However in John study recurrence rate 4 weeks after treatment in tinidazole tablet group (1 gram) was 22.5%, in tinidazole tablet group (500 mg) was 30.2% and in metronidazole tablet group was 33.3%.[16] Based on the criteria developed by Amsel *et al.* (1983), diagnosis of BV is made by identifying three of following four findings: 1) Thin, dark or dull gray, homogenous discharge 2) Vaginal pH (≥ 4.5) 3) Positive whiff test 4) Presence of clue cells on wet smear microscopic evaluation. These criteria have a sensitivity of 90% and a positive predictive value of 90%. Two treatment regimens in decreasing the homogenous vaginal discharge had a same effect and there was not significantly different across treatment groups ($p>0.05$).

Two weeks after treatment in tinidazole group 80.8% of patients and in metronidazole group 83.3% of patients had normal vaginal discharge. Based on a study by Raphael *et al.*[21] 4 weeks after treatment with tinidazole (2 g single dose + lactobacilli), 18.8% of patients had an abnormal discharge that is comparable to our study result. Also Kadohoris *et al* stated that all Gardenerella vaginosis cases responded to metronidazole, but in 25.9% cases vaginal discharge remained.[24] Whiff test is one of the Amsel criteria for diagnosing of BV with sensitivity of 93.3% and specificity 86.9%.[22] The study showed a same increase in number of patients with negative whiff test for two groups and 2 weeks after treatment 84.6% in tinidazole group and 83.3% in metronidazole group whiff test was negative. In Raphael *et al* study 4 weeks after treatment, 18.1% of patients had a positive whiff test that is comparable to this study results.[21]

Clue cells are vaginal epithelial cells that have a stippled appearance due to adherent Coco bacilli. The presence of clue cells more than 20% of the epithelial cells on wet smear is significant for BV. Clue cells with sensitivity of 76.7% and specificity of 92.4% are the most valuable criteria for diagnosis of BV.[22]

In the present study, both drugs were effective in reducing the Clue cells. Two weeks after treatment, 90.4% of cases in the tinidazole group and 91.7% of cases in the metronidazole group had less than 20% clue cells in their vaginal secretions. Based on Abbaspoor *et al* study after treatment with metronidazole gel, 60% had less than 20% clue cells in their vaginal secretions.[13] The difference between the two study results could be due to the drug form has used by patients and the duration of follow-up, in Abbaspoor study metronidazole vaginal gel was used and follow-up performed one week after treatment but in present study oral metronidazole was used and followed for two weeks after treatment.

Vaginal discharge acidity is the other Amsel criteria for diagnosing of BV with sensitivity 88.3% and specificity 58.6% in the diagnosis of BV.[22] In the present study, both drugs were effective in reducing vaginal pH. Two weeks after treatment in tinidazole group, 78.8% of cases and in metronidazole group, 70.8% of cases had a normal pH(less than 4.5). In Raphael *et al* study 4 weeks after treatment with tinidazole + lactobacilli, 28.1% of cases had a vaginal pH more than 4.5.[21]

Five and 0.8% of cases who received tinidazole had minimal side effects like drowsiness and metallic taste. In metronidazole group 20.8% cases reported some side effects like dark urine, metallic taste and drowsiness. John *et al* reported that no significant difference in terms of side effects between the two drugs.[16,25]

We concluded that tinidazole table 2 g once daily for 2 days in treatment of BV is safe and as effective as metronidazole tablet 500 mg twice a day for 7 days in treatment of BV. Also tinidazole compare to metronidazole with less side effects could make earlier cure feeling in patients. Therefore, it can be offered as an alternative for oral metronidazole in the treatment of BV.

Acknowledgements

We wish to thank Mohammad Hossin Haghighizadeh, MSc in statistics, Department of Statistics and Mathematics, for his full and helpful comments and in the statistical analysis. This paper was prepared from the thesis of Zeinab Rabee, and financial support was provided by Ahvaz Jundishapur University of Medical Sciences.

References

1. Berek JS, Novak E. *Berek and Novak's gynecology.* Vol 2007: Lippincott Williams & Wilkins; 2007.
2. Gibs K, Heni, Nigard. *Gynecological diseases Danfours.* 2010.

3. Yaghmai M, Arbabi colati F, Jahantigh M. Components of the amsel criteria for the diagnosis of bacterial vaginosis. *J Obstetrics, Gynecology and Infertility*. 2010;12(3):17-22.
4. Menard J-P. Antibacterial treatment of bacterial vaginosis: current and emerging therapies. *International Journal of Women's Health*. 2011;3:295.
5. Marrazzo JM, Antonio M, Agnew K, Hillier SL. Distribution of genital Lactobacillus strains shared by female sex partners. *Journal of Infectious Diseases*. 2009;199(5):680-683.
6. Ganjei L, Frohesh tehrani H, Mozafari N. Prevalence of Chlamydia cervicitis coincided with bacterial vaginosis. *J Ghom University of Medical Science*. 2010;1(5):3-6.
7. Ganjooie A, Shahabi M. Epidemiology and predisposing factor for bacterial vaginosis in patients with gynecologic in shahid bahonar hospital Kerman University. *J Kerman University of Medical Science*. 2004;10(4):200-210.
8. Martinez RC, Franceschini SA, Patta MC, Quintana SM, Gomes BC, De Martinis ECP, *et al*. Improved cure of bacterial vaginosis with single dose of tinidazole (2 g), Lactobacillus rhamnosus GR-1, and Lactobacillus reuteri RC-14: a randomized, double-blind, placebo-controlled trial. *Canadian Journal of Microbiology*. 2009;55(2):133-138.
9. Parhizgar A. Prevalence of symptomatic vaginal infections and their association with contraceptive methods. *Quarterly J Kurdistan University of Medical Sciences*. 2003;1:20-2.1
10. Martin HL, Richardson BA, Nyange PM, Lavreys L, Hillier, SL, Chohan B, *et al*. Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *Journal of Infectious Diseases*. 1999;180(6):1863-1868.
11. Pirotta M, Fethers KA, Bradshaw CS. Bacterial vaginosis-More questions than answers. *Australian family physician*. 2009;38(6):394.
12. CU-Uvin S, Hogan J, Caliend A, Harwell J, Mayer KH. Association between bacterial vaginosis and expression of human immunodeficiency virus type IRNA in female genital tract. *Clin.Infect.Dis*. 2001;33:896.
13. Geller M, Nelson A. Diagnosis and treatment of recurrent and persistent vaginitis. *Women's health in Primary Care*. 2003;6:537-540,545.
14. Mosavi Z, Behrozi R. Comparison of clindamycin and oral metronidazole for treatment of bacterial vaginosis. *Medical J of Gilan university* 2004;12(48):25-32.
15. Abbaspoor Z, Goodarzy F, Abbaspoor M. Comparison of the effectiveness of vitamin C vaginal tablet with metronidazole vaginal gel in the treatment of bacterial vaginosis. *African Journal of Pharmacy and Pharmacology*. 2010;4(7):484-489.
16. Fallah M, Rabiee S, Moshtaghi AA. Comparison between efficacy of single dose of tinidazole with a 7-day standard dose course of metronidazole in giardiasis. *PAKISTAN JOURNAL OF MEDICAL SCIENCES*. 2007;23(1):43.
17. Armstrong NR, Wilson JD. Tinidazole in the treatment of bacterial vaginosis. *International journal of women's health*. 2009;1:59.
18. Schwebke JR, Desmond RA. Tinidazole vs metronidazole for the treatment of bacterial vaginosis. *American journal of obstetrics and gynecology*. 2011;204(3):211. e211-211. e216.
19. Thulkar J, Kriplani A, Agarwal N. A comparative study of oral single dose of metronidazole, tinidazole, secnidazole and ornidazole in bacterial vaginosis. *Indian journal of pharmacology*. 2012;44(2):243.
20. Livengood III CH. Bacterial vaginosis: an overview for 2009. *Reviews in obstetrics and Gynecology*. 2009;2(1):28.
21. Thomason j, Scaglion Nj. *bacterial vaginosis. In: Mead PB,Hager WD, Faro S (eds). Protocol for infectious diseases in science Inc., 2000; 270-277*. 2000.
22. Kaufman R, Faro S. Benign Diseases of the Vulva and Vagina Mosby Year Book, St. *Louis, Missouri*. 1994.
23. Boskey E, Telsch K, Whaley K, Moench T, Cone R. Acid production by vaginal flora in vitro is consistent with the rate and extent of vaginal acidification. *Infection and immunity*. 1999;67(10):5170-5175.
24. Chaudhuri M, Chatterjee B. Pathogenic potential of Gardnerella vaginalis on the female urogenital system .*Journal of the Indian Medical Association*. 1996;94(1):11.
25. Decena DCD, Co JT, Manalastas RM, Palaypayon EP, Padolina CS, Sison JM, *et al*. Metronidazole with Lactacyd vaginal gel in bacterial vaginosis. *Journal of Obstetrics and Gynaecology Research*. 2006;32(2):243-251.