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A Clinical Study to Assess the Effectiveness of Oral Combination Kit Therapy in Syndromic Management of Abnormal Vaginal Discharge (FEMINE Study) in Kinshasa, Democratic Republic of Congo

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Abstract

Background: Vaginal discharge is one of most common and nagging problems that women face. About 20% - 25% of women who visit gynecology department complain of vaginal discharge and leucorrhoea. An orally administered combination kit, containing 2 g secnidazole, 1 g azithromycin and 150 mg fluconazole (Azimyn FS Kit), has been successfully evaluated in clinical trials and used in several countries for management syndromic vaginal discharge due to infections. ***Methods***: This is a longitudinal study which aimed to verify the clinical efficacy of the combined oral kit containing secnidazole, azithromycin and fluconazole (Azimyn FS Kit®) in the syndromic treatment of abnormal vaginal discharge in patients received in outpatient consultations in Kinshasa/DR Congo from March to September 2023. ***Results***: Majority of patients had whitish vaginal discharge (51.6%) of average abundance (56.2%), accompanied by pruritus in 72.1% of cases, and dyspareunia in 23.5% of cases and hypogastralgia in 40.2% of cases. One week after treatment with the Azimyn FS® combined kit, at the greatest majority of patients (97.3%), abnormal vaginal discharge had decreased by more than 50% (84.1%). Two weeks after treatment with the Azimyn FS® combined kit, almost all patients

(97.3%) no longer had abnormal vaginal discharge which had completely disappeared. ***Conclusion***: A single dose of secnidazole, azithromycin and fluconazole in the form of an oral combi-kit (Azimyn FS Kit) has shown excellent therapeutic effectiveness in the syndromic treatment of abnormal vaginal discharge wherein patients were treated without diagnostic confirmation.

Keywords

Oral Combination Kit Therapy, Syndromic Management, Abnormal Vaginal Discharge

1. Background

Vaginal discharge is one of most common and nagging problems that women face. About 20% - 25% of women who visit gynecology department complain of vaginal discharge and leucorrhoea. Although in a few cases the discharge may be a physiological increase in normal vaginal secretion, in over 60% of cases it is due to infection of the vagina and/or cervix [1]. *Trichomonas vaginalis*, bacterial vaginosis and *Candida albicans* are the most common causes of pathological vaginal discharge. Thus, all women with vaginal discharge should receive treatment for these infections [2] [3].

Vaginal discharge is often polymicrobial, and treatment of only one cause or most apparent cause can lead to a flare and clinical manifestations of the other cause. Thus, it is important to treat vaginal discharge as a syndrome rather than most clinically apparent cause or disease [4].

In syndromic management, diagnosis and treatment are not based on a specific disease-based test, but rather on syndromes, *i.e.* a group of clinical findings in patient. Treatment is usually given for most diseases that could cause this syndrome [5]. Physicians often prescribe one or more antimicrobials of their choice based on clinical experience, which may not adequately cover microbial flora [4] [6].

Anti-infective treatment combining several molecules administered separately has shown many limitations related to prolonged duration of intake in addition to side effects. An orally administered combination kit, containing 2 g secnidazole, 1 g azithromycin and 150 mg fluconazole (Azimyn FS Kit), has been successfully evaluated in clinical trials and used in several countries for the management syndromic vaginal discharge due to infections. Trichomoniasis and bacterial vaginosis can be treated with secnidazole given in a single 2 g dose which has better patient tolerability and compliance. It has a longer half-life and a longer duration of action. It is more cost effective with fewer side effects compared to metronidazole given for five days. Fluconazole increases adherence and is the only oral medication recommended by the US Centers for Disease Control in a single starting dose of 150 milligrams [7] [8].

It is well tolerated and cost effective unlike vaginal creams or suppositories containing clotrimazole or miconazole, which are often inconvenient and diffi-

cult to accept due to various cultural, religious and social factors. Chlamydia and gonorrhea are routinely treated with antibiotics of the tetracycline or penicillin group, which are administered in several doses. This causes poor patient compliance and missed doses leading to relapse [7] [8].

However, with the advent of macrolide Azithromycin, a single 1-gram dose has shown excellent cure rates. It is important to treat these two diseases in vaginal discharge because 70% of chlamydia trachomatis infections and 30% of gonococcal infections are asymptomatic and remain untransmitted in women [8] [9]. The Oral Combination Kit (Azimyn FS Kit) offers the convenience of a one-day treatment compared to other multi-dose treatments, which will also ensure the patient's high compliance with the treatment, thus increasing the chances of desired results [10] [11].

Due to its widespread use, it is proposed to evaluate effectiveness of this oral combination kit therapy in management of vaginal discharge in population of our environment in Democratic Republic of Congo (DRC) received in outpatient consultation. The expensive lab tests and associated waiting period for result result in the patient being left untreated while waiting for the test results. Therefore, by adopting a syndromic management approach, patient's eligibility for treatment will be decided based on abnormal vaginal discharge, its characteristics, severity, and other symptomatic presentations. This syndromic approach will help reduce the financial burden on the patient and will also avoid loss of patients during follow-up.

Objective of this study was to investigate the clinical efficacy of the combined oral kit containing secnidazole, azithromycin and fluconazole (Azimyn FS Kit®) in the syndromic treatment of abnormal vaginal discharge in patients seen in outpatient clinics in the DRC.

2. Methods

This is a longitudinal study which aimed to verify clinical efficacy of combined oral kit containing secnidazole, azithromycin and fluconazole (Azimyn FS Kit®) in syndromic treatment of abnormal vaginal discharge in patients received in outpatient consultations in health facilities in DR Congo selected by lot as well as in some hospitals in Kinshasa, Democratic Republic of Congo. Choice of hospitals was made randomly but taking into account the ease of access for us and fact that they are frequented by a category of poor patients for most part.

Study took place from March to September 2023. Sampling was set up consecutively for all women seen on an outpatient basis with abnormal vaginal discharge suspected of vaginal infection and who were prescribed combination oral kit Azimyn FS Kit®. This study was carried out according to the Helsinki recommendations. Eligible women were recruited after obtaining informed written consent to participate in the study.

2.1. Study Variables and Subject Monitoring

1) Sociodemographic, anthropometric and clinical variables: age, marital sta-

tus, weight, height, body mass index (BMI) calculated from weight and height, educational level, socio-economic level defined by patient's possession score according to the Adjusted Poverty Index (API).

2) History: menstruation, parity, pregnancy, abortion, sexually transmitted infection, sexually transmitted infection in partner.

3) Clinical parameters: type of vaginal discharge, severity of vaginal discharge and other symptoms (pruritus, dyspareunia, hypogastralgia, urinary symptoms), Clinical improvement determined by resolution of abnormal vaginal discharge and associated symptoms, tolerance of treatment determined by absence of side effects, recurrence determined by reappearance of abnormal vaginal discharge after resolution under treatment.

2.2. Selection and Enrollment Procedures

After written consent, for each patient admitted to study, collection of information (sociodemographic data, history and clinical data) was done by interview during outpatient consultation (visit 1). After presumptive diagnosis based on the appearance and abundance of abnormal vaginal discharge and associated symptoms, patient was started on one-day treatment with Azimyn FS kit containing fluconazole 150 mg 1 tablet, azithromycin 1 g 1 tablet and secnidazole 1 g 2 tablets. A first appointment after treatment was be given to him after one week for a clinical evaluation in order to note whether clinical improvement as well as tolerance of treatment. A second appointment after two weeks was making it possible to note whether there is a recurrence.

2.3. Statistical Calculations

Data were entered using Microsoft Excel 2007 software and exported to an SPSS 22.0 for Windows database for analysis. Descriptive statistics such as calculation of proportions as well as mean and standard deviation were used. For normally distributed parametric data, comparison of means was made using Student's t test or the ANOVA test as appropriate. And comparison of proportions was made using Pearson's Chi-square test or Fisher's Exact test. Tests were declared significant at $p < 0.05$.

3. Results

During the study, we recorded 498 consultations due to abnormal vaginal discharge.

3.1. General Characteristics of Population

General characteristics of population noted are age, level of education and marital status. The results of the analysis of these characteristics are presented in Table 1.

Analysis of general characteristics of our population, presented in Table 2 above, it appears that majority of patients, *i.e.* 61.6%, had an age between 20%

Table 1. Distribution according to general characteristics.

Characteristics	Effective (n = 498)	%	Average (min-max)
Age range			
≤19	27	5.4	
20 - 34	307	61.6	31.8 ± 9.5 years (15 - 69)
≥35	164	32.9	
Level of study			
Illiterate	10	2	
Primary	40	8	
Secondary	231	46.4	
University	217	43.6	
Marital status			
Single	215	43.2	
Divorcee	26	5.2	
Married	257	51.6	

and 34%. The average age in our series was 31.8 ± 9.5 years with extremes of 15 and 69 years. Majority of patients seen for consultation for abnormal vaginal discharge had a secondary education level, *i.e.* 46.4%, and were married, *i.e.* 51.6%.

3.2. Clinical Characteristics

1) General clinic

Clinical characteristics of population noted during general physical examination are weight, body mass index (BMI), parity, gestation and history of abortion. Results of the analysis of these characteristics are presented in Table 2.

From these general clinical characteristics, we noted an average body weight of 67.1 ± 12.1 kg with extremes of 44 and 125 kg. Vast majority had a weight less than 90 kg (96.6%). BMI was on average 25.1 ± 5.5 Kg/m^2 with extremes of 14 - 62 Kg/m^2. Mean parity and mean gestation were both 2 ± 2 with extremes of 0 and 12 for parity, and 0 and 14 for gestation. Patients with a history of abortion represented 23.5%.

2) Characteristics related to vaginal discharge

Characteristics related to abnormal vaginal discharge noted in population studied are history of sexually transmitted infections (STIs), type or appearance of vaginal discharge, severity of vaginal discharge as well as the associated symptoms (pruritus, dyspareunia and hypogastralgia). Results of the analysis of these characteristics are presented in Table 3.

After clinical examination at first consultation, the elements noted and analyzed, results of which are presented in Table 3, show us that majority, *i.e.* 66.3%

Table 2. Distribution according to general clinical characteristics.

Characteristics	Effective (n = 498)	%	Mean (min-max)
Body weight			
<90 Kg	481	96.6	67.1 ± 12.1 Kg (44 - 125)
≥90 Kg	17	3.4	
BMI (Kg/m²)			
Thinness (<18)	22	4.4	
Normal (18 - 24)	238	47.8	25.1 ± 5.5 Kg/m² (14 - 62)
Overweight (25 - 29)	162	32.5	
Obesity (≥30)	76	15,3	
Parity			
Nullipara (0)	236	47.4	
Primiparous (1)	80	16.1	2 ± 2 (0 - 12)
Pauciparous (2 - 3)	102	20.5	
Multiparous (≥4)	80	16.1	
Gestity			
Nulligest (0)	212	42.6	
Primigest (1)	68	13.7	2 ± 2 (0 - 14)
Paucigest (2 - 3)	99	19.9	
Multigesture (≥4)	119	23.9	
History of abortion			
No	381	76.5	
Yes	117	23.5	

Table 3. Distribution according to characteristics of vaginal discharge.

Characteristics	Effective (n = 498)	%
History of STIs		
Yes	330	66.3
No	168	33.7
Type of vaginal discharge		
Whitish	257	51.6
Yellowish	174	34.9
Purulent and smelly	47	9.4
Greenish and foamy	20	4
Abundance of vaginal discharge		
Not very abundant	134	26.9

Continued

Moderately abundant	280	56.2
Abundant	84	16.9
Associated symptoms		
Pruritus	359	72.1
Dyspareunia	117	23.5
Hypogastralgia	200	40.2

of patients seen for consultations for abnormal vaginal discharge had a history of sexually transmitted infection. From characteristics of this abnormal vaginal discharge, it emerged that majority of patients had whitish vaginal discharge, *i.e.* 51.6%, of average abundance, *i.e.* 56.2%, accompanied by pruritus in 72.1% of cases, and dyspareunia in 23.5% of cases and hypogastralgia in 40.2% of cases.

3.3. Evaluation of Treatment Based on Combined Kit

All patients received one day's treatment with the kit containing fluconazole 1 tablet of 150 mg, azithromycin 1 tablet of 1 g and secnidazole 2 tablets of 1 g (Azimyn FS®). A first appointment after treatment was given after one week for a clinical evaluation and to note whether clinical improvement as well as the tolerance of treatment, a second appointment after two weeks to note if there is a recurrence.

1) Elements noted at first appointment one week after treatment with Combined Kit

At the first visit or appointment, one week after treatment, we were interested in noting number of patients who presented, reduction in vaginal discharge and associated symptoms as well as the adverse effects of treatment. Results of the analysis of all these elements are reported in **Table 4**, **Figure 1** and **Figure 2**.

It emerges from the analysis of the elements noted at first appointment one week after treatment with the Azimyn FS® combined kit and presented in **Table 4**, that the greatest majority of patients, *i.e.* 97.3%, had responded to the appointment; abnormal vaginal discharge had decreased by more than 50% in vast majority of patients, *i.e.* in 84.1% of cases. And among them, 10.3% of patients had complete disappearance of abnormal vaginal discharge one week after treatment with the Azimyn FS® combined kit. Symptoms associated with this abnormal vaginal discharge, pruritus had disappeared in vast majority of cases after treatment with the Azimyn FS® combined kit, *i.e.* in 73.2% of cases; dyspareunia had disappeared in the majority of cases, *i.e.* 68.1%; as well as hypogastralgia which also disappeared in the majority of cases 64.7%.

When asked about the adverse effects of the medication received, patients presented, as shown in **Figure 1**, adverse effects in only 31.5% of cases. And its adverse effects were dominated, as presented in **Figure 2**, by nausea in 18.1% of cases, followed by metallic taste in 12.7% of cases and anorexia in 10.6%

Table 4. Distribution according to the elements noted at first appointment one week after treatment with combined kit.

Elements noted	Effective (n = 498)	%
Patient who attended the appointment		
Yes	485	97.3
No	13	2.7
Reductions in vaginal discharge in %	**n = 485**	
Disappearance	50	10.3
Reduction ≥ 50%	358	73.8
Reduction < 50%	77	15.9
Reductions of pruritus		
Disappearance	355	73.2
Reduction ≥ 50%	96	19.8
Reduction < 50%	34	7
Reductions of dyspareunias		
Disappearance	335	68.1
Reduction ≥ 50%	86	17.7
Reduction < 50%	64	13.2
Reductions of hypogastralgias		
Disappearance	314	64.7
Reduction ≥ 50%	112	23.1
Reduction < 50%	59	12.2

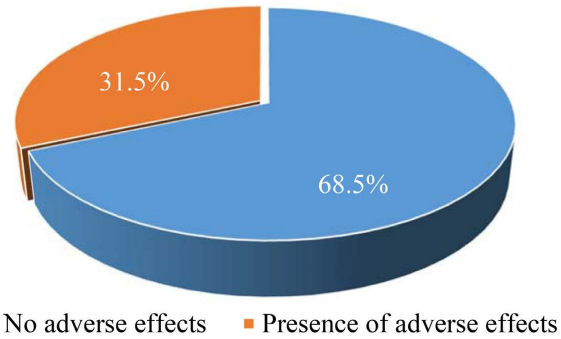

Figure 1. Presence of adverse effects of treatment based on combination kit.

of cases.

2) Elements noted at second appointment two weeks after treatment with Combined Kit

At second appointment which took place two weeks after treatment based on combined kit, objective was to evaluate, after noting number of patients who presented, disappearance of vaginal discharge and associated symptoms, recur-

rence rate of vaginal discharge and associated symptoms as well as their severity. The related results are presented in Table 5 and Figure 3.

Table 5, shows that largest majority of patients, *i.e.* 97.7%, also presented for third visit, *i.e.* two weeks after first and therefore after treatment with the Azimyn FS® combined kit. Almost all patients, *i.e.* 97.3%, no longer had abnormal vaginal discharge which had completely disappeared; only 2.7% had a recurrence. The same is true for symptoms associated with this abnormal vaginal discharge; they had completely disappeared in almost all cases, *i.e.* 98.9% for pruritus, 98.7% for dyspareunia and hypogastralgia, respectively.

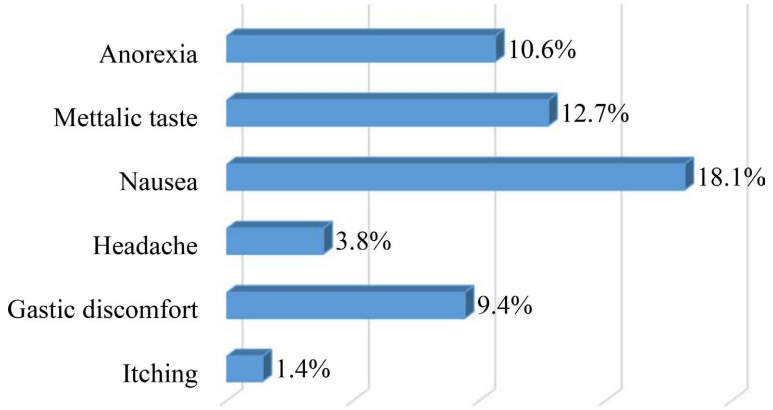

Figure 2. Types of adverse effects noted from combination kit treatment.

Table 5. Distribution according to the elements noted at second appointment two weeks after treatment with combined kit.

Elements noted	Effective (n = 485)	%
Patient who attended the appointment		
Yes	474	97.7
No	11	2.3
Vaginal discharge in %	**n = 474**	
Disappearance	461	97.3
Recurrence	13	2.7
Pruritus		
Disappearance	469	98.9
Recurrence	5	1.1
Dyspareunia		
Disappearance	468	98.7
Recurrence	6	1.3
Hypogastralgia		
Disappearance	468	98.7
Recurrence	6	1.3

3) Presence of adverse effects of treatment based on the Combined Kit two weeks later

Regarding the adverse effects of drug, we only noted them in 0.4% of cases two weeks after taking treatment (**Figure 3**). And of its adverse effects, only itching of skin and gastric discomfort were each reported in only 0.2% of cases (**Figure 4**).

4) Types of adverse effects of treatment based on Combination Kit noted

4. Discussion

Vaginal discharge is a major problem faced by women of reproductive age [12]. Their management in low-income countries generally depends on syndromic approach, which limits the understanding of specific causative agents. Targeted management is based on identifying causative organism and targeting therapy against it, while syndromic management is based on presence of elevated risk factors [2] [3]. Expensive laboratory tests and the associated, in our environment, waiting period for test results in patient remaining without treatment while awaiting test results [4]. Thus the oral combination kit (Azimyn FS Kit) offers convenience of one-day treatment compared to other multi-dose treatments, which

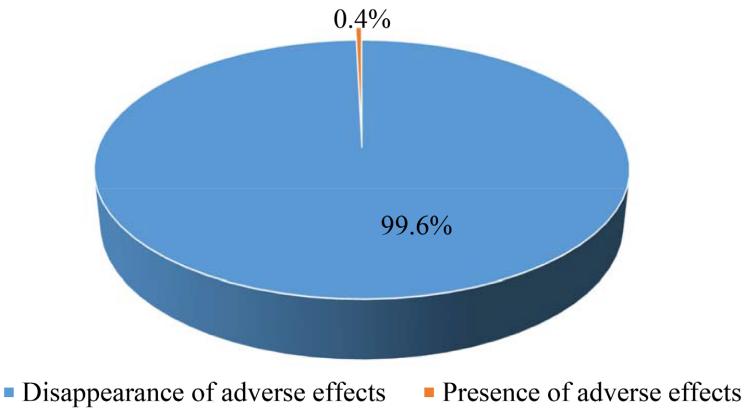

Figure 3. Presence of adverse effects of treatment based on the Combination Kit 2 weeks later.

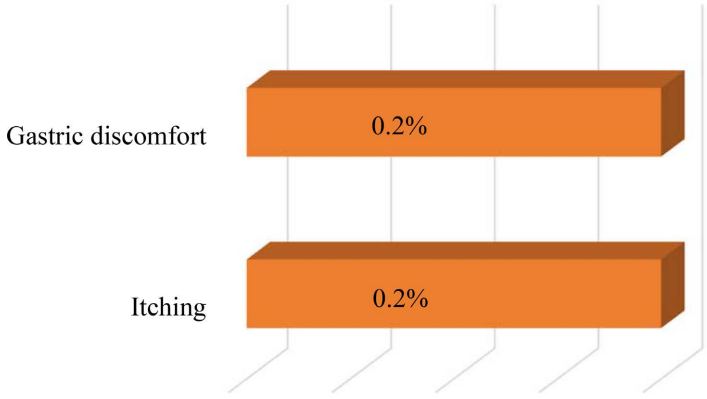

Figure 4. Types of adverse effects of treatment based on Combination Kit noted 2 weeks later.

also ensures high patient compliance to treatment, thereby increasing chances of desired results.

The prevalence of vaginal discharge in this age group is similar to those found by other authors in Africa and outside Africa where most represented age group was that included between 20 and 40 years [9] [13] [14] [15]. This age interval is the one where there is strong sexual activity and where hormonal impregnation is at its maximum activity [16].

Our study reported that majority of patients seen for consultation for abnormal vaginal discharge had a secondary education level for 46.4% and university education for 43.6%. The study conducted in Colombia also reports a majority of educated women, *i.e.* 58.49% [17]. Al Quaiz *et al.* also found a predominance of educated women [18]. Educated women are more likely to be aware of physiological and pathological vaginal discharge and therefore more likely to seek health care. Other authors, on the other hand, noted a majority of illiterate women, *i.e.* 69.9% for Majibo *et al.* [9], 74.9% for Dukers-Muijers *et al.* [19] and 56% for Venugopal *et al.* [20]. This difference can be explained by fact that our study and the one carried out in Colombia were carried out in an urban environment.

In our study, vaginal discharge was whitish in the majority of women, *i.e.* in 51.6% of them. Our results are similar to those found by Venugopal *et al.* [20], Fanou *et al.* [21], Sylla *et al.* [22] and Pizzorno *et al.* [23]. Whitish discharge is characteristic of vulvaginal candidiasis, and according to literature, latter remains one of main causes of abnormal vaginal discharge worldwide [1] [2] [3] [4] [9].

Vaginal discharge was moderately abundant in 56.2% of patients in our study. On the other hand, majority of authors noted abundant discharge in most of their patients [20] [21] [22]. This difference can be explained by subjective nature of this element which often depends on the assessment of person concerned and clinician.

Majority, 66.3% of patients seen for consultations for abnormal vaginal discharge had a history of sexually transmitted infection. Our results are largely different from those found elsewhere, notably by Hillier S *et al.* [24] who reported 38% and by Dukers-Muijers who reported 26.6% [19]. This difference can be explained by fact that our study population lives in a poor socio-economic environment with poor hygiene as well as promiscuity which could justify significant sexual activity for various purposes favoring these sexually transmitted infections.

Our study noted as main symptoms: vaginal discharge, followed by pruritus, hypogastralgia and dyspareunia in 100%, 72.1%, 40.2% and 23.5% respectively. Several studies have also reported these different symptoms associated mainly with abnormal vaginal discharge, notably Angel-Muller *et al.* [17] who found respectively 96.6%, 57.6% and 54.2% for vaginal discharge, bad odors and itching; Deka *et al.* [25] who found 91.5%, 88.2% and 59.6% for vaginal discharge, pruritus and abdominal pain respectively. These small differences are not statis-

tically significant, since vaginal discharge associated with pruritus and other symptoms constitute main symptomatology of vaginitis [2] [3] [4] [9] [12].

In the present study, the overall clinical cure rate with combination of secnidazole, azithromycin and fluconazole (Azimyn FS Kit) was around 98% from second week. Very high effectiveness reported in our study is close, although slightly higher, to the effectiveness reported in several studies, notably that of Deka *et al.* [25] who reported that in 705 patients clinically diagnosed with vaginitis, kit combined secnidazole, azithromycin and fluconazole has been shown to be effective. Similarly, another study carried out in India compared this combined kit of 3 molecules in a single dose to other combinations, 500 mg of ciprofloxacin and 600 mg of Tinidazole in 2 doses per day for 7 days on one side and 100 mg of doxycycline in 2 doses and 300 mg of metronidazole in 3 doses for 7 days on the other hand, and found an effectiveness of 93.5% revealing that there was no significant difference between the 3 groups [26]. Another study, on the other hand, carried out in Colombia and combining secnidazole with fluconazole as a treatment, noted cure rates of 90% to 94% depending on whether it was bacterial vaginosis or candidiasis [17]. This was also case for meta-analysis including only one secnidazole-based regimen, which compared 1 g versus 2 g and revealed clinical cure rates of 95.5% and 97.4% respectively [27]. Another study which rather evaluated the effectiveness of different molecules in treatment of chlamydia trachomatis found that single dose of azithromycin proved to be an effective and more practical treatment against STIs in women living in a poor environment [28]. In these latest studies, treatment was more directed against a specific germ after laboratory assessments, which was not case in our study which favored a syndromic approach. Several authors are unanimous that trichomonas vaginalis, vulvovaginal candidiasis, and bacterial vaginosis are most common causes of pathological vaginal discharge [4] [7] [29]. Thus, due to polymicrobial nature of abnormal vaginal discharge [30], combined kit based on secnidazole, Azithromycin and Fluconazole (Azimyn FS Kit) has a significant efficacy and safety profile.

Concerning safety of combination of secnidazole with azithromycin and fluconazole in a single oral dose (Azimyn FS Kit), no patient in our study presented serious adverse effects. Negligible adverse effects were recorded and were dominated mainly by gastrointestinal disturbances, notably nausea, followed by metallic taste and anorexia. The same adverse effects were reported by Angel-Muller *et al.* [17] and by Deka *et al.* [25]. The study conducted by Chawla *et al.* reported fewer adverse effects for a treatment consisting of secnidazole, azithromycin and fluconazole than in that of combinations between ciprofloxacin and tinidazole and between doxycycline and metronidazole [31]. Sharma *et al.*, comparing the effectiveness between combination of doxycycline and metronidazole to that between secnidazole, azithromycin and fluconazole, found more minor adverse effects in first group [32].

These adverse effects, more significant in other combinations, can be justified by presence of treatment lasting several days and with several daily doses. Al-

though our study did not use control groups treated with other molecules to compare therapeutic effectiveness of this kit, it appears that a single dose remains a good alternative.

5. Strengths and Limitation of the Study

This study is the first to be carried out in our environment, with a large sample and several targeted hospitals, it is one of rare studies to have the advantage of giving an overall overview of the effectiveness of this kit in our environment;

It demonstrated that treatment with Azimyn FS Kit significantly reduces cost of treating vaginal discharge with expected results, good acceptability and minor adverse effects.

But there was one limitation in our study, there should be point covering treatment of partner simultaneously

6. Conclusion

Vaginal discharge is often polymicrobial and hence, requires use of combi-kits, which are affordable, effective given as single dose orally allowing good compliance with complete treatment at the first visit. In this study, a single dose of secnidazole, azithromycin and fluconazole in the form of an oral combi-kit (Azimyn FS Kit) has shown excellent therapeutic effectiveness in the syndromic treatment of abnormal vaginal discharge wherein patients were treated without diagnostic confirmation. This approach will not only save time but also reduce the burden of laboratory testing.

Authors' Contributions

MFM and MAM are the main investigators. MAM generated and designed study. MFM participated in study design and will be actively involved in data collection. DMNRW, LAJ, NFM, MEPL, NBK, NNL, BJL, OCN, TUA, SMD and MRM contributed to drafting and improvement of manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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