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Prevalence and treatment outcome of vulvovaginal candidiasis in pregnancy in a rural community in Enugu State, Nigeria

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Vulvovaginal candidiasis (VVC) is a common condition, and an estimated 75 % of all women experience an infection with *candida* yeast during their lifetime. The study involved 901 pregnant women presenting to a rural hospital for ante-natal care within a period of ten months. Those with abnormal vaginal discharge or pruritus were screened for VVC. Those with symptomatic diagnosis of VVC were recruited for the cohort study after appropriate counseling and obtaining informed consent. Culture of high vaginal swab (HVS) and urinalysis were performed. Treatment of significant cases involved the use of nystatin and clotrimazole vaginal inserts. A total of four treatment groups (n = 157) were employed. Groups 1 and 2 received differently daily normal doses of the agents for 7 days respectively. Groups 3 and 4 received twice daily dosing of both agents for 7 days. In each case, the symptomatic response and re-culture of the HVS were repeated after treatment. Pharmacoeconomics of the two drugs was evaluated for the ten months period of the study and the prevalence of the VVC finally deduced. The result showed that the pregnant women had non-complicated VVC. Treatment outcome was generally the same with both nystatin and clotrimazole which invariably showed the same efficacy. In the first two groups, 72 % of those treated with once daily dosing of nystatin had their symptoms resolved within one week and 75 % achieved symptom resolution with clotrimazole during the same period. Some 96 % and 97 % of repeat culture of HVS for those that received twice daily dosing of the nystatin and clotrimazole had negative cultures respectively. The pharmacoeconomics of both agents reveal a remarkable difference in that a week treatment (once daily dosing) of nystatin costs ninety-one naira (N91. 00) which is less than $1 and clotrimazole for the same duration costs one hundred and sixty-eight naira (N168.00) which is $1.5. Going by cost minimization since both agents have similar outcomes, nystatin will naturally be selected. In the face of scarce resources, the costs and outcome analyses are valuable in therapeutic decisions.

Keywords: Vulvovaginal candidiasis; Prevalence; Pregnant women; Ante-natal; Nigeria**.**

INTRODUCTION

Vulvovaginal candidiasis (VVC) is a fungal infection of the female lower genital tract-the vulva and the vagina, caused by *Candida species* (Sobel, 2007; Nyirjesy et al., 2003; Marrazzo, 2002). It is also known as candidosis or moniliasis. VVC can be recurrent or relapsing (Ferris *et al.,* 2002; Nyirjesy, 2001). When a woman presents with four or more episodes per year, it is termed recurrent or relapsing VVC. Recurrent VVC is a condition that affects less than 5 % of healthy women (Rex et al., 2000).

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Candida species are part of the lower genital tract flora in 20-50 % of healthy asymptomatic women (McClelland *et al.,* 2009). Carrier rates are higher in women treated with broad spectrum antibiotics (Singh, 2003), pregnant women, diabetic women (Donders, 2002; de Leon et al., 2002) and women with HIV/AIDS (Reed *et al.,* 2003; Duerr et al., 2003). *Candida albicans* is both the most frequent colonizer and responsible for most cases of VVC (Singh, 2003). Nevertheless, over the last decades there have been reports demonstrating an increment in the frequency of cases caused by non-albicans species with *Candida glabrata* consistently being the leading species (Ray *et al.,* 2007; Ringdahl, 2000). The only well proven predisposing factors are pregnancy, diabetes mellitus (CDC, 2002), and the use of broad spectrum antibiotics (Mardh et al., 2002) as well as oral contraceptive with high oestogen content (Odds, 1988). Poorly supported risk factors include use of sponge, intrauterine devices (IUDS), diaphragms, condoms, orogenital sex, douching and intercourse (Mardh *et al.,* 2002, Reed et al., *2002*) and diet with high glucose content (de Leon et al., 2002).

An estimated 75 % of women will experience at least one episode of vulvovaginal candidiasis during their lifetime (Singh, 2003). In fact, 70 to 75 % of healthy adult women have at least one episode of VVC during their reproductive life and half of college women will, by the age of 25, have had one episode of VVC diagnosed by a physician (Sobel, 1997). Retrospective data reported during the early period of the AIDS pandemic suggested that the prevalence of VVC was increased in HIV-infected women compared to non-infected women (CDC, 2002). VVC is not considered a sexually transmitted disease (Singh, 2003), because it does affect celibate women and children and also *Candida species* is seen as normal vagina flora in healthy women. However, this does not mean that Candida cannot be sexually transmitted (de Leon et al., 2002, CDC, 2002; Mardh et al., 2002). Indeed, evidence in favour of sexual transmission exists. For instance, penile colonization is four times more frequent in male partners of women affected with VVC (McMclelland *et al.,* 2009; Rodin and Kolator, 1976) and infected partners commonly carry identical strains (O'connor and Sobel, 1986) which orogenital transmission has been documented (Markos *et al.,* 1992).

Diagnosis of VVC based solely on patients history and genital examination is not possible because of the low specificity of symptoms and signs since other causes mimic VVC like leucorrhoea and pruritus vulvae (Geiger *et al.,* 1995). Therefore, to have a positive (specific) diagnosis of VVC, a number of steps are recommended viz, determination of vaginal pH (normal 4-4.5) which means that a higher pH more than 5 is suggestive of bacterial vaginitis or trichomoniasis (CDC, 2002); preparation of a wet mount of the vagina discharge for identification of the yeast cells and mycelia and to rule out other diagnoses e.g. bacteria vaginosis and trichomoniasis (Marrazzo, 2002; CEG, 2002); a 10 % potassium hydroxide (KOH) preparation of vaginal discharge (Geiger et al., 1995). Gram stain preparation may also be used since yeast is gram-positive. If microscopic studies are negative and the index of suspicion of VVC continues to be high, vaginal swab for fungal culture is done (Sherrard, 2001; CEG, 2002; Sobel *et al.,* 1998). In all cases of pruritus vulvae, the urine should be tested for glucose (urinalyisis). The commonest cause of vulva pruritus in pregnancy is VVC which may be associated with the lowered renal threshold for sugar which occurs in pregnant women (Ten Teachers, 1997). The aim of the study was to assess the prevalence of VVC in a rural community in Enugu State and also to determine the pharmacoeconomics of the treatment outcome.

MATERIALS AND METHODS

Materials

The following materials used were nutrient agar, nutrient broth (International Diagnostic Group,UK), nystatin (Biomedicine, Belgium), clotrimazole (Drugfield Pharmaceuticals, Nigeria), Combi 9 multistix (Bohringer, Germany), sterile swab stick (Evepon Industries, Nigeria).

Methods

Preparation of culture media

The culture media were prepared according to the manufacturers specifications. Briefly, this involved weighing the appropriate quantity of each medium, dissolving in the stated solvent using heat and distribution into bijou bottles (20 ml) for sterilization in the autoclave at 121 ℃ for 90 min. The contents of the bottles were aseptically poured into the plates and allowed to set at room temperature. The solidified agar plates were used for the culture.

Study Area and Population

This study was carried out in a rural hospital, Nwa-Ossai Foundation Hospital, Orba Nsukka, Udenu L. G. A. of Enugu State, Nigeria. Orba is a commercial town that shares a common border with the University of Nigeria, Nsukka.

Pregnant women presenting to the hospital for ante-natal care between January-October 2007, with symptoms of vulvovaginal candidiasis (VVC) (abnormal vaginal discharge or pruritus) were screened for VVC. A total of 901 pregnant women attended the ante-natal care within this study period. Those with symptomatic diagnosis of VVC were recruited for the cohort study after appropriate counseling and obtaining informed consent. By means of personal interviews, their socio-demographic data were obtained. Culture of high vaginal swab (HVS) and urinalysis by dip stix method were used. Ab initio, they were instructed to be off all antibiotics three days prior to the day of collection of the HVS and urine specimens.

The study was in accordance with the ethical committee of the Enugu State Ministry of Health while informed oral consent was obtained from each participant.

Collection and processing of samples

Exposing the posterior fornix with a sterile vaginal speculum (Coscos), a sterile swab stick was inserted to pick a high vaginal swab. The swab stick was immediately replaced in its casing and labeled appropriately.

Urine specimen was collected using clean-catch midstream urine collection method. “Sterilin” Universal container was used to collect about 20 ml of urine sample per subject. Each specimen was refrigerated at 4 °C as soon as it was collected.

Inoculation, isolation and purification of the culture

Using a sterile platinum loop, each agar plate was aseptically inoculated with the HVS specimen. The plates were incubated at 37 °C for 24 h and thereafter observed for obvious microbial growth (colonies) on the surface of the culture plate.

Standard procedures (Sobel et al., 1998) were employed to identify and isolate the microbes there in. Subsequent sub-culturing in selected media was carried out to further purify the isolates.

Antibiotic sensitivity test for mixed growth

For each mixed isolate, sensitivity was determined using antibiotic discs after due subculturing. Briefly, the mixed isolates were seeded in agar plates, rotated in different directions and allowed to set at room temperature. Antibiotic discs were then placed on the set agar plates, allowed to equilibrate at room temperature for 15 min and finally incubated at 37 ^{o}C for 48 h. Thereafter, the plates were observed for obvious microbial growth (colonies) on the surface of the culture plate. Using Combi 9 multi stix, each urine sample was checked for proteinuria and sugar.

Treatment of significant cases

All significant cases of vulvovaginal candidiasis were subjected to chemotherapy. The subjects were divided into four groups (n = 157 per group). Two groups A and B received differently daily normal dosings of nystatin and clotrimazole vaginal inserts for 7 days respectively. Groups C and D received twice daily dosings of nystatin and clotrimazole for seven days respectively. In each case, the symptomatic response and re-culture of the HVS were repeated after treatment.

Pharmacoeconomics of the two drugs were also evaluated for the ten months period of study. The prevalence of the VVC was finally deduced from the record of all the ante-natal clients.

Follow-up procedure

At the end of the one week of chemotherapy, HVS and urinalysis were repeated and evaluated as earlier described. This was to perhaps determine the exact response (of the treated groups to the antimicrobial agents) as well as recurrence (relapse or re-infection) of the infection. Treated patients were seen weekly until delivery.

Stastical analysis

Differences between the treatment groups A-D were analyzed by ANOVA and Students t-test using SPSS version. Correlational analysis was performed with the Spearman rank correlation test. Results with values of $p<0.05$ were considered significant.

RESULTS

Screening for significant vulvovaginal candidiasis

Out of 901 pregnant women who attended antenatal clinic, 629 (70 ± 2.5 %) presented with symptoms of vaginal itching (pruritus vulvae) and discharge (leucorrhoea). A total of 560 (62.2 ± 7.5 %) of this number had positive culture of *Candida spp.* (significant VVC). Some 71 women who were symptomatic (pruritus and leucorrhoea) had negative cultures. This constituted about 7.7 ± 2.1 % of the studied population.

The remaining 270 (27.7 ± 5.0 %) were asymptomatic and were not subjected to laboratory diagnosis. The mean age of the study population was 29.8 years (S.D. 8.2 years). The results are summarized in Table 1.

Urinalysis

Of the 629 pregnant women screened, none had glucosuria. However, urinalysis was just a screening test for diabetes mellitus in pregnancy which is a predisposing factor for VVC (Geiger et al., 1995).

Treatment outcome of the patients (560) with positive culture was the same with both nystatin and clotrimazole showing that efficacy is invariably the same (Table 2). Out of 140 that received once daily dosing of nystatin 102 (72 %) had their symptoms resolved within the one week of treatment. Also, 106 (75 %) of those who received once daily dosing of clotrimazole had their symptoms resolved. Repeat cultures of HVS after one week of treatment with once daily dosing of nystatin and clotrimazole yielded some growth of *Candida* in 46 (33 %) and 44 (31 %) respectively.

The 142 pregnant women that received twice daily dosing of nystatin, had complaints (symptoms) at the end of the one week treatment and only 6 (4 %) yielded scanty growth of Candida on repeat culture. For clotrimazole, 5 (3 %) out of 138 that received twice daily dosing yielded scanty growth and all of them had their symptoms resolved within the one week of treatment.

Pharmacoeconomics of the therapeutic agents

Cost minimization analysis was used for the economic evaluation. Nystatin insertable tablets used for the study cost N13.00 per tablet X 7 nights i.e. N91.00 (less than $1) for once nocte course of treatment for one week. The cost of clotrimazole vaginal tablets was N24.00 per tablet i.e. N168.00 ($1.5) for once nocte course of treatment for one week. Deduction from the above shows that clotrimazole costs almost double that of nystatin.

In terms of side effects and tolerability on both mother and offspring, clotrimazole is preferred since there is no

Table 1. Prevalence of significant VVC in pregnant women

Parameter	No. of subjects	Percentage VVC (% ± S.D.)
Total attendance	901	100
Total screened	629	69.8 ± 10.5
Significant VVC (with positive culture)	560	62.2 ± 7.5
Symptomatic VVC (with negative culture)	71	7.9 ± 2.1
Asymptomatic VVC (unscreened)	270	29.97 ± 5

Table 2. Treatment outcome

Drug doses & duration of treatment (days)	Clinical outcome		Laboratory outcome	
	Resolved Symptoms	Symptoms not resolved	Negative culture	Positive culture
Nystatin 10,000 Units nocte X 7	102	38	94	46
Clotrimazole 100 mg nocte X 7	106	34	96	44
Nystatin 10,000 Units bid X 7	142	0	130	6
Clotrimazole 100 mg bid X 7	138	0	135	5

teratogenic effect after clotrimazole therapy during pregnancy (Czeizel et al., 1999). Besides, nystatin lacks controlled human studies making it difficult to establish its relative safety in pregnancy. However, the anxiety and fear created by the notion that nearly all drugs cause congenital abnormalities is more harmful than the effect of proven human teratogenic drugs themselves (Shehata and Nelson-Piercy, 2000; Czeizel, 1999).

DISCUSSION

The study showed high prevalence rates (62.2 %) of vulvovaginal candidiasis among pregnant women attending antenatal clinic over the period of ten (10) months in this rural community. About 70 % had clinical symptoms of VVC and as high as 62.2 % were microbiologically confirmed. Nikolov et al., (2006) reported 88.3 % prevalence by microscopy while Klufio et al., (1995) reported 57 % infection microbiologically. The high rates are in conformity with the fact that *Candida albicans* is both the most frequent colonizer and responsible for most cases of vulvovaginitis (Singh, 2003; Hainsworth, 2002; Watson al., 2001).

Some 7.7 % of the studied population had clinical symptoms – pruritus vulvae and leucorrhoea – without *Candida species* being isolated. The symptoms are not specific for Candida vulvovaginitis. For example, vaginal pruritus predicted Candida vulvovaginitis only 38 % of the time (Bergman, 1994). About 90 % of patients with vaginal discharge (leucorrhoea) suffer from infection of the vagina caused by *Candida, Gardnerella* or *Trichomonas* (Ray et al., 2007; Ten Teachers, 1997).

In another study, the prevalence of vaginal candidiasis in pregnant women was only 28 % with *Candida albicans* being implicated in more than 90 % of the cases (Garcia et al., 2004). The result of this study which agreed with an earlier observation (Sobel et al., 1996) is shown in Table 2. Candidiasis is often diagnosed on the basis of clinical features alone and as many as half of these women may have other conditions e.g. allergic reactions (Patel *et al.,* 2003; Berg *et al.,* 1984). Klufio et al., (1995) reported the prevalence of individual infections as *Trichomonas vaginalis* 19 %, *Candida albicans* 23 % and bacterial vaginosis 23 %. The rate which could be misdiagnosed as vulvovaginal candidiasis on clinical presentation alone is high and could be wrongly subjected to treatment. This highlights the need for laboratory diagnosis before commencing therapy.

The results of urinalysis of the 629 pregnant women screened showed no glucosuria. This implied that none of the candidates with VVC had diabetes, a known predisposing factor for increased rates of VVC (Vaquez and Sobel, 1995). Reduced renal threshold for sugar occurs in many pregnant women with many having glucosuria without being obviously diabetic (Ten Teachers, 1997). Increased glucose levels in the genital tissue enhance yeast adhesion and growth, and vaginal epithelial cells have a greater propensity to bind to *C. albicans* in women with diabetes than in those without diabetes (Bohannon, 1998).

Treatment outcome was generally the same with both nystatin and clotrimazole which invariably showed the same efficacy. Seventy-two percent (72 %) of those who received once daily dosing of nystatin had their symptoms resolved within one week and seventy-five (75 %) achieved symptom resolution during the same period with clotrimazole once daily dosing. This result was comparable to that by Reef et al., (1995) which showed that topical azoles and nystatin therapies gave 80 – 95 % and 70 – 90 % clinical and mycological cure rate respectively in vulvovaginal candidiasis. However, Young

and Jewel, (2001) found in their five trials that imidazoles were more effective than nystatin when treating vaginal candidiasis in pregnancy.

The result showed that repeat cultures of high vaginal swabs (HVS) after one week of treatment with once daily dosing of nystatin and clotrimazole yielded some growth of *Candida* in 41 % and 32 % cases respectively. On twice daily dosing for both nystatin and clotrimazole, there was symptom resolution within one week of therapy in all the patients and cultures yielded only scanty growth in 4 % for nystatin and 3 % for clotrimazole.

Young and Jewel, (2001) reported that single dose treatment was less effective than three or four days treatment when assessed by culture and by symptoms in three different trials, and treatment lasting for four days was less effective than treatment for seven days. They concluded that topical imidazole appears to be more effective than nystatin for treating symptomatic vaginal candidiasis in pregnancy with treatment lasting up to seven days.

Cost analysis of both agents (nystatin and clotrimazole) showed a remarkable difference. A week treatment (once daily dosing) of nystatin costs ninety-one naira (N91.00; less than $1) and clotrimazole for the same duration costing one hundred and sixty-eight naira (N168.00; $1.5). Generally, the azole antifungals are more expensive than nystatin. In the face of scarce resources, the costs and outcome analyses are valuable in therapeutic decisions.

CONCLUSIONS

The pregnant women in this study had non-complicated VVC. The study revealed that VVC among pregnant women in this locality was not uncommon so that continuous ante-natal screening should be an on-going exercise for all pregnant women with history of itching and vaginal discomfort. This will prevent further complications and even transmission to partners. Nystatin has a long-standing efficacy and is cheap but clotrimazole is equally effective but far more expensive. The study recommends that in the face of scarce resources, the old traditional cheap values should not be abandoned for more expensive new ones when both have similar outcomes.

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