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Vaginal infections in diabetic woman

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Abstract
Diabetes mellitus is a chronic disease that can affect any organ or system of the body. Diabetes mellitus has long been considered as one of the factors causing Candida vaginitis and has the potential to affect sexual function in women. Infectious diseases are more prevalent in individuals with Diabetes Mellitus. One of the problems of women with diabetes is resistant vulvovaginitis, which is related to some factors such as neuropathy, hyperglycemia, allergy and atopy. Women's interest in, satisfaction with, and ability to participate in sexual activity may be influenced globally by the effect of diabetes on their overall health, physical and mental functioning, and interpersonal relationships. Additionally, sexual function may be adversely affected by diabetes medications or other health interventions. This manuscript is a comprehensive review on vulvovaginal infections in diabetic patients.

Keywords: Diabetes, vulvovaginal infections, vaginitis, Candidiasis, recurrent infections, genital yeast infections, genital mycotic infections, fungal infections, sexual dysfunction.

Introduction

Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the produced insulin. This leads to an increased concentration of glucose in the blood (hyperglycemia). Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity. Gestational diabetes is hyperglycemia that is first recognized during pregnancy. 346 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of high blood sugar. WHO projects that diabetes death will double between 2005 and 2030 (WHO, 2011). Diabetes is characterized by elevated morbidity and mortality. Diabetes represents an economic burden, with serious implications for the public health systems. Accordingly, the need of effective tools aimed to the prevention of its chronic complications is urgent and cannot be deferred (Lavery et al. 1998, 157–62).

Besides the classical complications of the disease, DM has been associated with reduced response of T cells, neutrophil function, and disorders of humoral immunity (Geerlings and Hoepelman 1999, 259–65; Peleg et al. 2007, 3–13). Consequently, DM increases the susceptibility to infections, both the most common

ones as well as those that almost always affect only people with DM (e.g. rhino cerebral mucormycosis) (Peleg et al. 2007, 3–13). Such infections, in addition to the repercussions associated with its infectivity, may trigger DM complications such as hypoglycemia and ketoacidosis. Infectious diseases are more prevalent in individuals with DM. The main pathogenic mechanisms are hyperglycemic environment increasing the virulence of some pathogens; lower production of interleukins in response to infection; reduced chemotaxis and phagocytic activity, immobilization of polymorphonuclear leukocytes; glycosuria, gastrointestinal and urinary dysmotility. Some infections usually affect only diabetic persons, such as malignant external otitis, rhino cerebral mucormycosis, and gangrenous cholecystitis. In addition to being potentially more serious, infectious diseases in DM may result in metabolic complications such as hypoglycemia, ketoacidosis, and coma (Casqueiro, Casqueiro and Alves 2012, S27-36).

Diabetes causes short-term and long-term complications and usually its long-term complications develop 5 to 10 years after the diagnosis of both types of the disease (Smeltzer, S. Bare 2000). One of its long-term complications is a neurological complication that includes a disorder of sexual functioning. The autonomic system causes a wide range of disorders in all systems of our body including the urinary-sexual system. It can be said that sexual dysfunction develops frequently as a complication among these patients (Chu and Edelman 2002, 60–66). Neuropathy, vascular impairment, and psychological complications are involved in decreased libido, low arousal, decreased vaginal lubrication, orgasmic dysfunction, and dyspareunia among women with diabetes.

Moreover, one of the problems of women with diabetes is resistant vulvovaginitis, which is related to some factors such as hyperglycemia, allergy and atopy. One of the most common pathogens associated with this condition is Candida spp. (Malazy et al. 2007, 399–404).

Material and methods

The following sources were searched for the original study: The Cochrane Library, MEDLINE, EMBASE and the Cochrane sexually transmitted disease (2000-2014). Selection criteria were:

- Randomized controlled trials published in any language;
- Women (age 16 years or over) with uncomplicated vulvovaginal candidiasis;
- The vulvovaginal candidiasis to be made mycological (i.e. positive culture and/ or microscopy for yeast);
- The primary outcome measure was clinical cure.

Data collections and analysis

Two reviewers screened titles and abstract of the electronic search results and full text of potentially relevant papers. Two reviewers performed independent duplicate abstraction. Disagreements regarding trial inclusion or data abstraction were resolved by discussion between the reviewers. Odds ratios were pooled using the fixed effects models (except for two analyses when random effects models were used because of potentially important heterogeneity).

Normal vaginal flora

Anatomically, the female genital tract is constituted by a succession of cavities that communicate with exterior through the vulvar cleft. Vaginal microflora undoubtedly presents one of the most of important defense mechanism for the reproductive function, maintaining the environment healthy and preventing the proliferation of microorganisms, stranger to the vagina (Linhares, Giraldo and Baracat, 370–74). The different components of the vaginal ecosystem have been observed on the microscope and afterwards, identified through culture-specific techniques (Larsen and Monif 2001, e69-77). However, more recently, identification techniques for independent bacteria in the means of culture have revolutionized the study of microorganisms. The use of amplification, cloning techniques and subsequent analysis of sequences of bacterial genes (genes that codify for bacterial rRNA 16S) in sample of vaginal fluid have allowed the identification of the majority of common species of Lactobacilli and other microorganisms. Thus, these techniques have demonstrated that Lactobacilli spp. do not always correspond to the dominant species in the vagina of healthy women. Besides that, vagina environment inhabitants until then unknown have been identified (Zhou et al. 2004, 2565–73; Fredricks, Fiedler and Marrazzo 2005,

1899–1911). Although vaginal bacterial species of healthy women have been initially identified as Lactobacillus acidophilus, this knowledge represents a simplification, since in women whose flora is dominated by Lactobacillus, the more frequently detected species through genic amplification are L. crispatus and L. inners (Zhou et al. 2004, 2565–73; Fredricks, Fiedler and Marrazzo 2005, 1899–1911) or L. crispatus and L.gasseri (Verhelst et al. 2004, 16). Other species as. L. jensenii, L. gallinarum and L. vaginalis have also been identified in some women. A study on vaginal flora accomplished in three continents using method of bacterial genes analysis showed that dominant species were the same in each region: L. crispatus, L.gasseri and L. jensenii (Pavlova et al. 2002, 451–59) Besides, that, the same study observed that, in some women, the normal ecosystem was maintained in the absence of Lactobacillus; in one woman Atopobium vaginae was identified as the dominant microorganism in the flora and, in two other woman, the bacteria Atopobium, Megasphaera and Leptotrichia were all lactic acidic producers similarly Lactobacillus. (Zhou et al. 2004, 2565–73; Rodriguez Jovita et al. 1999, 1573–76). Therefore, other bacteria, not only by Lactobacillus, may keep the vagina's acidic environment, known as an important defense mechanism against the proliferation of pathogens. Characteristic of vaginal microbial flora is the presence of biofilms. Biofilms are formed by colonies of microorganisms that adhere among themselves and cover a solid surface. Biofilms have already been identified in the surface of vaginal cells, more known in women with bacterial vaginosis, where species of Gardnerella vaginalis and Atopobium predominate (Swidsinski et al. 2005, 1013–23). The occurrence of species of Lactobacilli producers of hydrogen peroxide, which possess a defense activity against pathogens, seems to be less frequent in African-American women (Antonio, Hawes and Hillier 1999, 1950–56). Studies suggest that for bacterial vaginosis-free women, the vaginal pH is higher in African-American women (Stevens-Simon et al., 168–72) they suggest also that such differences are valid only for women whose vaginal microflora is not dominated by Lactobacillus (Royce et al. 1999, 96–102; Fiscella and Klebanoff 2004, 747–50). The composition of the vaginal flora is not constant, suffering variations in response to exogenous and endogenous factors (Priestley et al. 1997, 23–28; David A. Eschenbach et al. 2001, 913–18). These factors include the different phase of menstrual cycle, gestation, use of contraceptives, frequency of sexual intercourse, use of showers or deodorant products, use of antibiotics or other medications with immune-suppressive properties. Alterations occurring in the vaginal environment may increase or decrease the selective advantages for specific microorganisms. For example, studies have related the loss of Lactobacillus to sexual intercourse or the use of antibiotics (Schwebke, Richey and Weiss2 1999, 1632–36).

Nevertheless, another study has demonstrated that the sexual act without the use of condom had o effects upon the Lactobacillus, but increase the level of Escherichia coli and facultative gram-negative bacilli (D A Eschenbach et al. 2000, 901–7).

During the menstrual cycle, hormonal variations interfere in the substrate of different microorganisms; these variations lead to change s in vaginal ph. Yet the levels of Lactobacillus remain constant throughout the cycle, the non-Lactobacillus bacteria increase during the proliferative phase and the concentrations of Candida albicans become higher in the premenstrual period (Witkin 1987, 34–37).

Candida albicans is tolerant to the acidic environment, fund in approximately 10% to 20% of women in reproductive age. The concentration of the microorganism is low, so the woman carrier is asymptomatic. Nevertheless, event leading to a state of local immune-suppression, such as sexual intercourse or local induction of allergic response, create adequate conditions for the proliferation of the microorganism and facilitate the transformation into the shape of hyphae, more invasive (Witkin 1987, 34–37) Furthermore, Candida albicans appears to be able to raise the pH from 4 to > 7, resulting in auto induction of yeast-hyphal transition as demonstrated in study of Vylkova et al. (Vylkova et al. 2011, e00055-11). When the hyphal form is predominant, it results in the emergence of symptomatic vaginitis. The production of lactic acid may be essential for the maintenance of healthy ecosystem, regardless of the bacterial species that may be present in the vagina. Resulting acidic pH prevents the excessive prolif-

eration of potentially pathogenic microorganisms. It is important yet to remember that the Lactobacillus dominance is beneficial for the host, since some species produce hydrogen peroxide and bacteriocins, factors that inhibit the proliferation of the other microorganisms. In addition to the protective effects of the endogenous vaginal flora, the protection against potentially pathogenic microorganisms is done also by the local components of innate immunity and acquired immunity. The epithelial cells layer of the vagina constitutes the initial contact point between microorganism and host's genital tract. These epithelial cells possess toll-like receptors (TRL) in their surface and, therefore, are important components of innate vaginal immunity (Quayle, 61–79). Vaginal cells also release molecules with potent non-specific antimicrobial activity. A class of these molecules, known as defensives, include positively charged peptides that rapidly bind negatively charged bacterial surface (Linhares, Giraldo and Baracat, 370–74).

Vulvovaginal diseases in diabetic woman

A. Candidiasis

One of the problems of women with diabetes is resistant vulvovaginitis, which is related to some factors such as hyperglycemia, allergy and atopy. One of the most common pathogens associated with this condition is Candida albicans. Thus, most physicians begin antifungal therapy at the patient's first visit, even without paraclinical findings. The prevalence of Candida spp. vulvovaginitis and factors that cause diabetic women to be prone to this infection were analyzed in a study of B. 160 women with diabetes mellitus (mean age, 51 - 10 years; age range, 16–75 years) were enrolled. Ninety-four percent of the patients had type II diabetes mellitus and the remaining had type I. Seventy-five percent of the participants received oral hypoglycemic drugs, 15% received insulin and the rest were given combination therapy (tablets plus insulin). The mean duration of diabetes mellitus in these patients was 9 - 6 years (range, 0.08–36 years). The subjects were mainly homemakers (92.5%), and the rest were workers. There was sexual activity in 86.3% of the cases, and none in 13.7% of the cases. Twenty-one percent of our patients had a history of allergy (rhinitis, sinusitis or atopic dermatitis) (Malazy et al. 2007, 399–404).

In this study, all subjects were asked to fill out prepared questionnaires on demographic characteristics, type of diabetes mellitus, duration and type of its treatment, past history of allergy, methods of washing underwear (detergents, heat, etc.) and voiding after sexual intercourse, and vaginal examination was done for each participant by a general physician. In addition, concentrations of fasting blood sugar, 2-hour postprandial blood sugar and glycosylated hemoglobin were measured, and cultures of vaginal discharge were performed.

71% (113/160) of the women had clinical vaginitis (fungal or bacterial), and 12.5% (20/160) had Candida vaginitis. Microscopic findings for Candida were positive in 12 patients, of whom two had Candida vaginitis.

The prevalence of Candida vaginitis together with positive culture was 2.6% (4/160). After including the 10 patients with positive Candida culture together with other clinical vaginitis, the overall prevalence of Candida vaginitis based on positive culture was 8.8% (14/160). There was a significant statistical difference between either mean fasting blood sugar or educational level and infectious vaginal culture. There were no significant associations between positive culture and age, glycosylated hemoglobin, history of allergy, genital hygiene, and occupation, kind of treatment, and type or duration of diabetes.

One of the complications experienced by diabetic patients is resistant and recurrent infections. Some believe that malfunctioning leucocytes, especially in the presence of uncontrolled blood glucose levels (Wilson and Reeves 1986, 478–84; Wilson, Tomlinson and Reeves, 37–40; Raith, Csató and Dobozy 1983, 557–64) cause the condition. Among the infections, vaginal inflammation or infection, especially fungal vaginitis, is more disturbing in severe hyperglycemic conditions (Foster 1998, 2060–81) The most common etiologic agent for this infection is the yeast (fungal) organism, usually Candida (Curry 1994, 689–700; Eckert et al. 1998, 757–65; Smith 1998, 557–58; Moraes 1998, 165–69; Bornstein et al. 2001, 105–11). In a study by Eckert et al (Eckert et al. 1998, 757–65) Candida was detected in 28% of cultures of vaginal discharge obtained during the initial visit of women with vaginitis; the remaining cultures

were for other organisms, such as sexually transmitted organisms. In this case, the authors believed that the causes of recurrent disease or resistance to therapy were false diagnosis of the pathogenic organism and unsuitable treatment (Eckert et al. 1998, 757–65). On the other hand, even when correct diagnosis had been made, background factors, especially those associated with systemic diseases like diabetes mellitus, caused treatment failure (Foster 1998, 2060–81; Smith 1998, 557–58). Researchers have stressed the importance of personal hygiene, history of infections and allergic diseases of the upper respiratory tract (nose, sinuses), and atopic dermatitis in the subject or the relative(s) in recurrent diseases or resistance to therapy (Moraes 1998, 165–69).

In this study, the authors stated that there are no significant statistical differences or relationship between positive vaginal Candida culture and type of diabetes mellitus, age, and glycosylated hemoglobin, duration of diabetes mellitus, history of allergy, occupation, genital hygiene and vaginal intercourse. Diabetes mellitus has long been considered as one of the factors causing Candida vaginitis (J D Sobel 1993, 153–65; Scudamore, Tooley and Allcorn 1992, 260–63). Different studies showed that symptomatic infection is more common in women with diabetes than in the normal population (J D Sobel 1993, 153–65; Scudamore, Tooley and Allcorn 1992, 260–63). The prevalence ranged from around 7% to more than 50% (Bohannon 1998, 451–56; Sonck and Somersalo 1963, 846–52; Davis 1969, 40–45) and most of which was attributed to Candida albicans (Duerr et al. 1997, 252–56; Otero et al. 1998, 526–30).

Two specialized clinics reported that the prevalence of vulvovaginitis caused by non-albicans species is around 10–20%, with Candida glabrata dominating (Jack D. Sobel 1997, 1896–1903; Spinillo et al. 1992, 343–47). Sobel et al (J D Sobel et al. 1998, 203–11) stated that the probable causes of higher non-albicans species: the short duration of use for oral or local anti-Candida regimens; widespread use of over-the-counter antifungal agents, most of which are used incorrectly or inadequately; and the prolonged use of antifungal compounds for the prevention of recurrent vulvovaginitis, which further intensifies the problem.

The control of blood glucose levels and a suitable antifungal therapy play an important role in controlling vaginal Candida spp. infection in diabetic women (Bohannon 1998, 451–56). In a study of 241 diabetic women, a significant statistical relationship existed between overall prevalence of vaginal infections (bacterial and fungal) and mean blood glucose level. In addition, it was suggested that glucose levels be maintained below 200 mg/dL to avoid dehydration, caloric loss and glycosuria and to reduce the risk of infection. The authors also found a significant statistical difference between mean fasting blood sugar and infectious culture of vaginal discharge ($p = 0.016$). It did not find a significant statistical difference between glycosylated hemoglobin and infectious vaginitis, because acute infections such as vaginitis often occur during the hyperglycemic state, but glycosylated hemoglobin reflects the mean blood glucose level over the previous 3 months.

Similar to the study by Mas Martin (R Goswami et al. 2000, 162–66) B also found that most of the patients with positive vaginal Candida culture (64%) were older than 45 years. Regarding the high prevalence of Candida vaginitis in reproductive ages (Spinillo et al. 1992, 343–47; Deepti Goswami et al. 2006, 111–17) and our lack of knowledge about the prevalence of this condition in non-diabetic women with similar age groups (16–75 years), it is suggested that further evaluation be conducted to determine the cause. In any case, the incidence of symptomatic infection

is high among reproductive ages (18–44 years) (de Leon et al. 2002, 1). Although it was reported that allergic rhinitis and recurrent Candida vaginitis were present concurrently in 70% of patients (Moraes 1998, 165–69) we did not find any relationship between Candida or non-Candida vaginitis and history of allergy (sinusitis, rhinitis or atopic dermatitis). According to our results, there was significant statistical difference between educational level and infectious or positive vaginal Candida culture.

Other factors involved in the pathogenesis of Candida vulvovaginitis include lifestyle factors. Although vulvovaginal candidiasis is more frequent among sexually active women (during the second decade of life) (de Leon et al. 2002, 1) it is not considered as a sexually transmitted disease (Jack D. Sobel 1997, 1896–1903) Candida

accounts for 20–50% of the normal vaginal flora of asymptomatic healthy women (Geiger, Foxman and Sobel 1995, 304–7) and Candida vaginitis can even occur in single women. Naturally, Candida is transmitted through vaginal sexual intercourse, as well as other modes of sexual contact.

There is controversy about the frequency of sexual intercourse as a risk factor of vaginitis. However, some studies showed that oral sex increases the incidence of vulvovaginal candidiasis and that vaginal intercourse alone cannot change the Candida colonization rates in the vagina (Malazy et al. 2007, 399–404).

Yeast development can be stimulated by glucose and even be promoted to change to a more virulent stage. Pregnancy and/or diabetes increase(s) the adherence of C. albicans to vaginal epithelial cells in vitro (Grigoriou et al. 2006, 121–25).

Women with type I diabetes had higher Candida colonization rates than those with type II, even after adjusting for age, behavioral factors and HbA1c.10 Whether this is due to the diabetes type or reflects the different distributions of Candida species by age or both remains unclear. With the oxidative killing ability of neutrophils hindered, diabetics may not be able to clear pathogens as efficiently as non-diabetics may. Hyperglycemic individuals may have increased risk for Candida colonization as their secretions contain glucose, which can serve as nutrients for Candida species. A fucose (6-deoxy-galactose) vaginal epithelial cell receptor that aids in adhesion of Candida to vaginal epithelial cells was reported.30 Fucose acts as one form of the receptor site for Candida adhesion; therefore, increased Candida colonization may be proportional to the glucose level. However, glycaemia does not fully explain the observed increased risk of Candida colonization. Grigoriou et al (Malazy et al. 2007, 399–404) found an increased prevalence of vaginal candidiasis in diabetic patients compared with non-diabetic patients. Likewise, C. albicans was isolated significantly more in diabetic patients than non-C. Albicans species (Yildirim, Kilic and Kalkanci 2011, e463-7).

Large proportion of vulvovaginal candidiasis (VVC) in diabetes is due to non–albicans Candida species such as C. glabrata and C. tropicalis. Observational studies indicate that diabetic patients with C. glabrata VVC respond poorly to azole drugs. It is evaluated the response to oral fluconazole and boric acidic vaginal suppositories in diabetic patients with VVC.

112 consecutive diabetic patients with VVC were block randomized to receive either single-dose oral 150-mg fluconazole or boric acidic vaginal suppositories (600 mg/day for 14 days). The primary efficacy outcome was the mycological cure in patients with C. glabrata VVC in the two treatment arms. The secondary outcomes were the mycological cure in C. albicans VVC, overall mycological cure irrespective of the type of Candida species, frequencies of yeast on direct microscopy, and clinical symptoms and signs of VVC on the 15th day of treatment. Intention-to treat (ITT; n = 111) and per protocol (PP; n = 99) analyses were performed.

C. glabrata was isolated in 68 (61.3%) and C. albicans in 32 (28.8%) of 111 subjects. Patients with C. glabrata VVC showed higher mycological cure with boric acidic compared with fluconazole in the ITT (21 of 33, 63.6% vs. 10 of 35, 28.6%; P = 0.01) and PP analyses (21 of 29, 72.4% vs. 10 of 30, 33.3%; P = 0.01). The secondary efficacy outcomes were not significantly different in the two treatment arms in the ITT and PP analyses.

Diabetic women with C. glabrata VVC show higher mycological cure with boric acidic vaginal suppositories given for 14 days in comparison with single-dose oral 150-mg fluconazole.

The 59.9% prevalence of C. glabrata infection observed in the current study confirms the findings of our earlier studies that non-albicans VVC is frequent in diabetic women (R Goswami et al. 2000, 162–66; Deepti Goswami et al. 2006, 111–17). De Leon et al (de Leon et al. 2002, 1) observed the 54% vaginal carriage rate of C. glabrata in type 2 diabetes. The comparable frequency of clinical symptoms and signs between diabetic women with C. glabrata or C. albicans infection is similar to that reported by Geiger et al (Geiger, Foxman and Sobel 1995, 304–7) in nondiabetic women.

Increased prevalence of C. glabrata infection in diabetic women has clinical relevance because poor therapeutic response and innate resistance to azoles has been reported for C. glabrata VVC in nondiabetic women (Vermitsky and Edlind 2004, 3773–81) Similar information is

lacking in diabetic subjects, as they are often excluded in antifungal efficacy studies (Deepti Goswami et al. 2006, 111–17) Poor mycological cure in diabetic women with C. glabrata VVC to single-dose oral 150-mg fluconazole, observed in the current study, is in accordance with our earlier case-control study (Deepti Goswami et al. 2006, 111–17). In the current study, the higher mycological cure (72.4%) to boric acidic therapy in diabetics with C. glabrata VVC is similar to that reported in nondiabetic individuals.

Boric acidic or boracic [B (OH) $_3$] is a weak acidic, and its mode of antifungal action is not clear. Shiohara and Tasker (15) proposed that its acidic properties lead to disruption of the fungal cell wall. The cause of increased C. glabrata isolation in diabetic women is not clear but may involve frequent use of antifungal drugs leading to its reduced susceptibility to azoles (Ruhnke 2006, 495–504) and consequent polarization/homing in diabetic women. Feng et al (Feng et al. 2005, 445–50) reported lesser susceptibility of C. glabrata in comparison with Albicans to β-defensins, natural cationic antimicrobial/antifungal peptides expressed in human epithelia. In diabetic milieu, β-defensins expression is reduced (Froy et al. 2007, 796–802). Reduced expression of defensins in association with resistance of C. glabrata to fungicidal activity of drugs like fluconazole may also explain the high prevalence of C. glabrata VVC in diabetic women. Boric acidic therapy could be considered as the frontline therapy for treating VVC in diabetic women because it is effective against both C. albicans and C. glabrata compared with fluconazole, which is effective against C. albicans only (Ray et al. 2007, 312–17).

Sertaconazole nitrate is a new topical broad-spectrum antifungal that was developed to provide an additional agent for the treatment of superficial cutaneous and mucosal infections. Sertaconazole has been tested in vitro against clinical and laboratory isolates of the most common fungi present in superficial tinea and Candida infections. Sertaconazole is effective against a broad spectrum of organisms that cause superficial cutaneous fungal infections.

Clinical trials with Sertaconazole nitrate cream 2% show efficacy in the treatment of superficial cutaneous fungal infections (Zsolt I. 2002, 29-32). In European clinical studies of other dermatomycoses caused by Candida spp., Sertaconazole was shown to be superior to other azoles and terbinafine.

Sertaconazole nitrate has been tested with a variety of in vitro methods, all of which show fungistatic activity against dermatophytes and fungicidal and fungistatic activity against yeasts (Carrillo-Muñoz et al. 2003, 248–51).

In a similar study, Day (Grossman and Day 2005, P128) showed that over a 48-h exposure period, approximately 38% of the applied dose, or 800 Ag, penetrated the skin. These results are considerably higher than the concentrations (MICs) required in susceptibility studies to eradicate fungal growth in vitro. Thus, a short course of treatment with Sertaconazole for 4 weeks will give ratios of Cmax/MIC N1000 for dermatophytes and Candida. This level of exposure should be sufficient to obtain successful mycological cure rates of the major dermatophytes and yeas that cause superficial fungal infections; however, at present, there is insufficient data relating clinical outcome to drug exposure and MIC to allow us to assign a predictive value to these parameters. In immunocompetent patients, the majority of uncomplicated, superficial mycoses are yeast and tinea infections, caused mainly by Candida spp. and dermatophytes, respectively (Pfaller and Sutton 2006, 147–52).

The most common vulvovaginal symptom especially during candidiasis include irritation, burning, erythema and sometimes dyspareunia (Lewis et al. 2010, 1598–1607). In particular itching is reported as the more discomfort symptom (Nowosielski and Skrzypulec-Plinta 2011, 2532–45).

B. Sexual / Libido diseases

Diabetic women often deal with low sexual desire, orgasmic dysfunction, dyspareunia, and sexual aversion along with decreased lubrication often related to neuropathy.

Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs.

About 60 to 70 percent of people with diabetes have some form of neuropathy. People with diabetes

can develop nerve problems at any time, but risk rises with age and longer duration of diabetes. The
highest rates of neuropathy are among people who have had diabetes for at least 25 years.
Hyperglycemia and oxidative stress also contribute to the abnormal glycation of nerve cell proteins and the inappropriate activation of protein kinase C, resulting in further nerve dysfunction and ischemia.
However, more recent large epidemiological studies conducted on women in the United States, Brazil, and Australia did not find a significant relationship between diabetes, desire, arousal, or orgasm. In diabetic women, hypertension or the use of hypertensive drugs seem to be associated with orgasm and lubrication dysfunction as well as decreased sexual interest. Stress urinary incontinence is negatively associated with all aspects of women's sexual dysfunction (sexual interest, desire, arousal, lubrication, and orgasm), and is positively correlated with dyspareunia and vaginismus (Lewis et al. 2010, 1598–1607).
Sexual function was examined in a cross-sectional cohort of ethnically diverse women aged 40 to 80 years using self-administered questionnaires. Multivariable regression models compared self-reported sexual desire, frequency of sexual activity, overall sexual satisfaction, and specific sexual problems (difficulty with lubrication, arousal, orgasm, or pain) among insulin-treated diabetic, noninsulin-treated diabetic and nondiabetic women. Additional models assessed relationships between diabetic end-organ complications (heart disease, stroke, renal dysfunction, and peripheral neuropathy) and sexual function.
Among the 2,270 participants, mean SD age was 55 ± 9.2 years, 1,006 (44.4%) were non-Latina white, 486 (21.4%) had diabetes, and 139 (6.1%) were taking insulin. Compared to 19.3% of non-diabetic women, 34.9% of insulin-treated diabetic women (adjusted OR [95%CI] =2.04[1.32–3.15] and 26.0% of non-insulin-treated diabetic women (adjusted OR [95%CI] =1.42[1.03–1.94]) reported low overall sexual satisfaction. Among sexually active women, insulin-treated diabetic women were more likely to report problems with lubrication (OR [95%CI] =2.37[1.35–4.16]) and orgasm (OR [95%CI] =1.80[1.01–3.20]) than nondiabetic women. Among all diabetic women, end-organ complications such as heart disease, stroke, renal dysfunction, and peripheral neuropathy were associated with decreased sexual function in at least one domain. Compared to nondiabetic women, diabetic women are more likely to report low overall sexual satisfaction. Insulin-treated diabetic women also appear at higher risk for problems such as difficulty with lubrication and orgasm. Prevention of end-organ complications may be important in preserving sexual activity and function in diabetic women.
For the purposes of analysis, participants were categorized into one of three-diabetes status groups based on whether they had diabetes, and, if so, whether they were using insulin: (1) insulin-treated diabetic women, (2) non-insulin-treated diabetic women, and (3) non-diabetic women. These categories were chosen a priori based on the recognition that insulin use is a widely recognized indicator of diabetes severity and represents a higher level of disease management burden that can interfere with day-to-day functioning and quality of life.
Differences in the demographic and clinical characteristics of participants in these three categories were examined using chi-square tests for categorical variables and analysis of covariance for continuous variables. Next, it is described the distribution of less than monthly sexual activity, less than moderate sexual desire, and less than moderate sexual satisfaction among women in each diabetes status category. Among women reporting at least some sexual activity in the past 3 months, the prevalence of specific sexual problems such as low or very low arousal, at least moderate difficulty with lubrication, at least moderate difficulty with orgasm, or at least moderate pain with vaginal intercourse were also examined among women in each diabetes status category. Differences in the distribution of these sexual function outcomes among women in different diabetes status categories were examined using chi-square tests.
Multivariable logistic regression models compared sexual function outcomes among: (1) insulin-treated diabetic versus nondiabetic women, and (2) noninsulin-treated diabetic versus nondiabetic women, adjusting for a core set of other factors with potential to influence sexual function (i.e., age, race/ethnicity, marital/relationship status, menopausal status, his-

tory of sex with men or women, body mass index, hysterectomy and oophorectomy, selective serotonin reuptake inhibitor [SSRI] use, and estrogen use.) While models examining frequency of sexual activity, desire, and satisfaction included all women, models examining specific sexual problems were confined to sexually active women, and additionally controlled for frequency of sexual activity.

Sexual activity, desire, and satisfaction outcomes were examined in all diabetic participants, while specific problems with lubrication, arousal, orgasm, or pain were examined in sexually active diabetic women only.

Of the 2,270 participants, 139 (6.1%) were insulin-treated diabetic, 347 (15.3%) were noninsulin-treated diabetic, and 1,784 (78.6%) were non-diabetic women. Mean (± SD) age was 55 (± 9.2) years, 1,006 (44.4%) were non-Latina white, 443 (19.5%) were African-American, 401 (17.7%) were Latina, 401 (17.7%) were Asian, and 18 (0.8%) were Native American. Overall, 63.7% of participants reported some sexual activity in the past 3 months. Of the 807 women who reported no sexual activity in the past 3 months, 271 (33.6%) indicated that lack of a partner and 224 (27.7%) indicated that partner health problems contributed to their sexual inactivity.

Insulin-treated diabetic women were less likely to report at least monthly sexual activity compared to either non-insulin-treated diabetic women or non-diabetic women. Insulin-treated diabetic women were also more likely to report low sexual desire and satisfaction compared to non-insulin-treated diabetic women or non-diabetic women (Nowosielski and Skrzypulec-Plinta 2011, 2532–45).

Among sexually active participants, problems with lubrication were also more common in insulin-treated diabetic women compared to non-diabetic women (Carati et al. 2013, 2668–74).

Among sexually active women, insulin-treated diabetic women were also more than twice as likely to report difficulty with lubrication and 80% more likely to report difficulty-achieving orgasm compared to non-diabetic women, after adjusting for the same demographic and clinical factors. When asked if their physical health limited their sexual activity, insulin-treated diabetic women were more likely than non-diabetic women to report that their health limited their sexual activity "quite a bit" or "extremely," in multivariable analysis (OR[95%CI] = 2.29[1.49–3.51]). However, non-insulin-treated diabetic women were not substantially more likely than non-diabetic women to feel that their health limited their sexual activity (OR [95% CI] = 1.29 [0.92–1.78]).

Diabetic women with peripheral neuropathy were also more likely to report less than monthly sexual activity, lower sexual desire, and limitation of sexual activity by physical health, compared to those without neuropathy. Among sexually active diabetic women, no significant associations between specific diabetic end-organ complications and sexual problems such as difficulty with arousal, lubrication, orgasm, or pain with intercourse were observed in adjusted models. There were also no significant associations between number of years since diabetes diagnosis and sexual function, after adjustment for end-organ complications ($P > 0.05$ for all).

In this cohort of ethnically diverse middle-aged and older women, diabetic and non-diabetic women reported similar levels of sexual desire and frequency of sexual activity, after adjustment for other demographic and clinical factors. However, both insulin-treated and non-insulin-treated diabetic women were significantly more likely to report low overall sexual satisfaction compared to non-diabetic women, and problems with lubrication and orgasm were more common among insulin-treated diabetic women compared to nondiabetic women. These findings suggest that while many diabetic women are interested and engaged in sexual activity, diabetes is associated with a markedly decreased sexual quality of life in women, either through complications of the disease itself or through utilization of treatments.

This study underlines the importance of distinguishing between different aspects of female sexual function when evaluating the burden of this disease. Based on this research, diabetes and its complications appear to have a much greater impact on sexual problems such as lubrication and orgasm as opposed to sexual desire or subjective arousal. Furthermore, our study indicates that the adverse effects of diabetes on sexual function may be concentrated in women taking insulin, an apparently high-risk group for developing sexual problems.

Diabetic women who were less motivated or interested in checking and controlling their blood sugars may have placed more priority on sexual activity and/or function in their daily lives, resulting in higher reports of sexual satisfaction. Alternatively, diabetic women with worse glycemic control may have had lower expectations about sexual activity in the setting of their poorly controlled disease, with the paradoxical result that they retained a stronger subjective sense of sexual satisfaction in spite of experiencing the same sexual difficulties. Differences in impulse control and other unmeasured personality factors could also have influenced both glycemic control and sexual satisfaction in diabetic participants.

Based on this research, clinicians may want to consider actively assessing for sexual problems in diabetic women, particularly those taking insulin, and counsel diabetic women that prevention of end-organ complications may be important in preserving their sexual function (Copeland et al. 2012, 331–40).

In Jordanian's study women were grouped into a diabetic married group (n = 613) and a nondiabetic married group (n = 524). The age of diabetic women ranged from 23 to 68 years (mean ± SD 46 ± 11 years), and the age of nondiabetic women ranged from 22 to 70 (51 ± 10 years). The prevalence of FSD in diabetic women 50 years of age or older was significantly higher compared with that in nondiabetic women. Desire, arousal, lubrication, and orgasm were more significantly affected in older diabetic women, whereas in younger women a significant difference was only found in desire. Multivariate analysis showed that glycemic control, type of diabetes, smoking, hypertension, dyslipidemia, and peripheral and autonomic neuropathy did not have a significant effect on FSD. On the other hand, longer duration of diabetes, older age, higher BMI, and the presence of coronary artery disease, nephropathy, and retinopathy had significant detrimental effects on female sexual function. This study shows that diabetic women in Jordan have more FSD than nondiabetic women. The prevalence of FSD in our study is in agreement with the global prevalence (Erol et al. 2002, 55–62) Neurovascular processes that mediate genital vasocongestion are impaired in diabetes (Meston and Frohlich 2001, 603–9) In this study, vaginal dryness was found significantly more often-in diabetic women than in nondiabetic women. Orgasmic dysfunction was more prevalent in older diabetic women in comparison with their nondiabetic counterparts. Kolodny reported a higher frequency of orgasmic dysfunction in diabetic women than in hospitalized women for various reasons (Enzlin et al. 2002, 672–77).

However, diabetic women were less satisfied with their sexual life. This is in agreement with the findings of Enzlin et al (Abu Ali et al. 2008, 1580–81).

Neuropathy, vascular impairment, and psychological complaints have been implicated in the pathogenesis of decreased libido, low arousability, decreased vaginal lubrication, orgasmic dysfunction, and dyspareunia among diabetic women. A cross-sectional study was conducted on 500 women who were recruited from a diabetes center, based on questionnaires completed by them. Data regarding demographic features, physical complications, and sexual disorders were obtained. Medical records of patients were used to obtain body mass index (BMI) and details of complications. Mean age of participants, duration of diabetes, and BMI was 48.8 ± 0.4, 8.9 ± 0.32 years, and 28.9 ± 0.23, respectively. Prevalence of sexual dysfunction was 32.3%. Low sexual desire was seen in 81.8%, disorders of arousal in 78.3%, of orgasm in 47.5%, and 35.1% had disorder in resolution area. There was no significant relationship between some factors such as age, duration of diabetes, BMI, and frequency of sexual dysfunction. Frequency of diabetic complications demonstrated a significant effect on the prevalence of sexual dysfunction. Sexual problems are frequent among diabetic women and deserve more attention in clinical practice and researches.

In a research conducted by Amini et al (Omidvar et al. 2013, 321–24) in Isfahan in 2001, a low sexual desire, lack of sexual satisfaction, low vaginal lubrication, and orgasmic dysfunction have been recognized as sexual problems among women. For every patient with diabetes who refers with a reduction in sexual desire, first other reasons (hormonal reasons and so on) should be ruled out, and then neuropathic; therefore, the genital organ should be examined, and the levels of testosterone, prolactin, thyrotropin, and estrogen should be

checked. Sexual dysfunction among women with diabetes includes vaginal dryness, a low sense of perinea, a lack of orgasm, and so on. The average age of the subjects, duration of married life, number of children, duration of diabetes, and body mass index (BMI) were 48.8 ± 0.04 years, 29.6 ± 0.5 years, 4.2 ± 0.1, 8.9 ± 0.3 years, and 28.9 ± 0.2, respectively. The results show a significant frequency of sexual dysfunction in different sexual areas. Majority (95%) of the subjects were suffering from type 2 diabetes; 26.3% of them mentioned a severe pain during sexual intercourse. In this study, there was no association between age, diabetes duration, and BMI with frequency of sexual dysfunction, although there was a significant association between age and dysfunction in desire ($P = 0.02$), sexual satisfaction ($P = 0.01$), and pain during intercourse ($P = 0.004$). It is found a significant statistical association between the number of complications due to diabetes and frequency of sexual dysfunction ($P = 0.01$). Overall, sexual dysfunction among women with diabetes was 32.3%. Nearly 82% of them were afflicted in the area of dysfunction in sexual desire, 78.3% had problems of arousal, 47.5% experienced dysfunction in orgasm, and 35.1% in the area of resolution. In all, 45.5% were not satisfied with sexual functioning. 39.4% experienced pain during intercourse, and 36.1% had disorders in vaginal lubrication. Previous reports have shown an increase in the prevalence of sexual dysfunction among women with type 1 diabetes (Omidvar et al. 2013, 321–24).

Conclusion

Diabetic women with end-organ complications such as peripheral neuropathy, renal dysfunction, stroke and heart disease were more likely to report decreased sexual activity or lower sexual satisfaction than diabetic women without these complications.

Several studies suggest the presence of sexual dysfunction among those who suffer from type two diabetes (Omidvar et al. 2013, 321–24; Bultrini et al. 2004, 337–40). These disorders include disorders of desire, lubrication, satisfaction, orgasm, and dyspareunia. The etiology of sexual dysfunction in patients with diabetes needs more attention because patients with diabetes are at risk for vascular and psychological complications. Therefore, they have a higher risk for developing sexual dysfunction (Fatemi and Taghavi 2009, 38–39).

These findings suggest that diabetic end-organ complications may play an important role in decreasing women's sexual quality of life, and that raise the possibility that prevention of diabetic complications may be helpful in preventing sexual dysfunction in women with diabetes.

The steps to be taken are clear: campaigns aimed at

(1) Prevention of type 2 diabetes

(2) Screening for early diabetic disease

(3) Increasing patient awareness of vulvovaginal disease

(4) Using medications of proven strategy and finally

(5) Researching and trialing of new therapies.

The ultimate challenge is to get action from primary health care to all higher levels; from the individual patient, to those at risk, in various health jurisdictions, in all countries despite varying economic circumstances and priorities. The problem is a global one and yet requires action at a local level; prevention, screening, and treatment strategies; education, including increasing awareness both in diabetic patients and those at risk of developing diabetes; and health priorities of governments. Basic research and clinical trials searching for a new understanding and therapies must be supported. It is time for strategies that prevent diabetes and its sequelae. It is time for programs for health care workers to diagnose and treat people with diabetic vulvovaginal disease, starting from basic hygiene that should be practiced with specific product, with specific active addressed to improve moisturisation, lubrication of the intimate area and able to exert a soothing action in case of irritability and itching.

References

- Abu Ali, Ruba M, Rabaa M Al Hajeri, Yousef S Khader, Nadima S Shegem and Kamel M Ajlouni. Sexual Dysfunction in Jordanian Diabetic Women. *Diabetes Care* 31, no 8 (2008), 1580–81. doi:10.2337/dc08-0081.
- Antonio, M A, S E Hawes and S L Hillier. The Identification of Vaginal

Lactobacillus Species and the Demographic and Microbiologic Characteristics of Women Colonized by These Species. *The Journal of Infectious Diseases* 180, no 6 (1999), 1950–56. doi:10.1086/315109.

- Bohannon, N J. Treatment of Vulvovaginal Candidiasis in Patients with Diabetes. *Diabetes Care* 21, no 3 (1998), 451–56.
- Bornstein, J, Y Lakovsky, I Lavi, A Bar-Am and H Abramovici. The Classic Approach to Diagnosis of Vulvovaginitis: A Critical Analysis. *Infectious Diseases in Obstetrics and Gynecology* 9, no 2 (2001), 105–11. doi:10.1155/S1064744901000187.
- Bultrini, Antonella, Eleonora Carosa, Elisabetta M Colpi, Gianfranco Poccia, Rossella Iannarelli, Danilo Lembo, Andrea Lenzi and Emmanuele A Jannini. Possible Correlation between Type 1 Diabetes Mellitus and Female Sexual Dysfunction: Case Report and Literature Review. *The Journal of Sexual Medicine* 1, no 3 (2004), 337–40. doi:10.1111/j.1743-6109.04048.x.
- Carati, D, M Guido, A Malvasi, A Zizza and A Tinelli. Efficacy of a Dermoxen® Lenitiva for Pruritus Genitalis in a Randomized, Double Blind Trial. *European Review for Medical and Pharmacological Sciences* 17, no 19 (2013), 2668–74.
- Carrillo-Muñoz, A J, B Fernández-Torres, D C Cárdenes and J Guarro. In Vitro Activity of Sertaconazole against Dermatophyte Isolates with Reduced Fluconazole Susceptibility. *Chemotherapy* 49, no 5 (2003), 248–51. doi:72449.
- Casqueiro, Juliana, Janine Casqueiro and Cresio Alves. Infections in Patients with Diabetes Mellitus: A Review of Pathogenesis. *Indian Journal of Endocrinology and Metabolism* 16 Suppl 1, no 7 (2012), S27-36. doi:10.4103/2230-8210.94253.
- Chu, Neelima V and Steven V Edelman. Erectile Dysfunction and Diabetes. *Current Diabetes Reports* 2, no 1 (2002), 60–66.
- Copeland, Kelli L, Jeanette S Brown, Jennifer M Creasman, Stephen K Van Den Eeden, Leslee L Subak, David H Thom, Assiamira Ferrara and Alison J Huang. Diabetes Mellitus and Sexual Function in Middle-Aged and Older Women. *Obstetrics and Gynecology* 120, no 2 Pt 1 (2012), 331–40. doi:10.1097/AOG.0b013e31825ec5fa.
- Curry, S.L. Barclay D.L. Benign Disorders of the Vulva and Vagina. Dans *Current Obstetric and Gynecologic Diagnosis and Treatment*. Sous la direction de AH DeCherney, 8th editio., 689–700. Norwalk, Connecticut: Appleton and Lange, 1994.
- Davis, B A. Vaginal Moniliasis in Private Practice. *Obstetrics and Gynecology* 34, no 1 (1969), 40–45.
- de Leon, Ella M, Scott J Jacober, Jack D Sobel and Betsy Foxman. Prevalence and Risk Factors for Vaginal Candida Colonization in Women with Type 1 and Type 2 Diabetes. *BMC Infectious Diseases* 2 (2002), 1.
- Duerr, A, M F Sierra, J Feldman, L M Clarke, I Ehrlich and J DeHovitz. Immune Compromise and Prevalence of Candida Vulvovaginitis in Human Immunodeficiency Virus-Infected Women. *Obstetrics and Gynecology* 90, no 2 (1997), 252–56. doi:10.1016/S0029-7844(97)00253-6.
- Eckert, L O, S E Hawes, C E Stevens, L A Koutsky, D A Eschenbach and K K Holmes. Vulvovaginal Candidiasis: Clinical Manifestations, Risk Factors, Management Algorithm. *Obstetrics and Gynecology* 92, no 5 (1998), 757–65.
- Enzlin, Paul, Chantal Mathieu, Annick Van den Bruel, Jan Bosteels, Dirk Vanderschueren and Koen Demyttenaere. Sexual Dysfunction in Women with Type 1 Diabetes: A Controlled Study. *Diabetes Care* 25, no 4 (2002), 672–77.
- Erol, Bulent, Ahmet Tefekli, Isa Ozbey, Fatih Salman, Nevin Dincag, Ates Kadioglu and Sedat Tellaloglu. Sexual Dysfunction in Type II Diabetic Females: A Comparative Study. *Journal of Sex & Marital Therapy* 28 Suppl 1, no

sup1 (2002), 55–62. doi:10.1080/00926230252851195.

- Eschenbach, D A, S S Thwin, D L Patton, T M Hooton, A E Stapleton, K Agnew, C Winter, A Meier and W E Stamm. Influence of the Normal Menstrual Cycle on Vaginal Tissue, Discharge, and Microflora. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America* 30, no 6 (2000), 901–7. doi:10.1086/313818.
- Eschenbach, David A., Dorothy L. Patton, Thomas M. Hooton, Amalia S. Meier, Ann Stapleton, Jan Aura and Kathy Agnew. Effects of Vaginal Intercourse with and without a Condom on Vaginal Flora and Vaginal Epithelium. *The Journal of Infectious Diseases* 183, no 6 (2001), 913–18. doi:10.1086/319251.
- Fatemi, Seyedeh Seddigeh and Seyed Morteza Taghavi. Evaluation of Sexual Function in Women with Type 2 Diabetes Mellitus. *Diabetes and Vascular Disease Research* 6, no 1 (2009), 38–39. doi:10.3132/dvdr.2009.07.
- Feng, Z, B Jiang, J Chandra, M Ghannoum, S Nelson and A Weinberg. Human Beta-Defensins: Differential Activity against Candidal Species and Regulation by Candida Albicans. *Journal of Dental Research* 84, no 5 (2005), 445–50. doi:10.1177/154405910508400509.
- Fiscella, Kevin and Mark A Klebanoff. Are Racial Differences in Vaginal pH Explained by Vaginal Flora? *American Journal of Obstetrics and Gynecology* 191, no 3 (2004), 747–50. doi:10.1016/j.ajog.2004.03.032.
- Foster, D.W. Diabetes Mellitus. Dans *Harrisons's Principles of Internal Medicine*. Sous la direction de E. Isselbacher KJ Fauci, AS Braunwald, 14th Editi., 2060–81. New York: McGraw-Hill, 1998.
- Fredricks, David N, Tina L Fiedler and Jeanne M Marrazzo. Molecular Identification of Bacteria Associated with Bacterial Vaginosis. *The New England Journal of Medicine* 353, no 18 (2005), 1899–1911. doi:10.1056/NEJMoa043802.
- Froy, Oren, Amit Hananel, Nava Chapnik and Zecharia Madar. Differential Effect of Insulin Treatment on Decreased Levels of Beta-Defensins and Toll-like Receptors in Diabetic Rats. *Molecular Immunology* 44, no 5 (2007), 796–802. doi:10.1016/j.molimm.2006.04.009.
- Geerlings, S E and A I Hoepelman. Immune Dysfunction in Patients with Diabetes Mellitus (DM). *FEMS Immunology and Medical Microbiology* 26, no 3–4 (1999), 259–65.
- Geiger, A M, B Foxman and J D Sobel. Chronic Vulvovaginal Candidiasis: Characteristics of Women with Candida Albicans, C Glabrata and No Candida. *Genitourinary Medicine* 71, no 5 (1995), 304–7.
- Goswami, Deepti, Ravinder Goswami, Uma Banerjee, Vatsla Dadhwal, Sunita Miglani, Ali Abdul Lattif and Narayana Kochupillai. Pattern of Candida Species Isolated from Patients with Diabetes Mellitus and Vulvovaginal Candidiasis and Their Response to Single Dose Oral Fluconazole Therapy. *The Journal of Infection* 52, no 2 (2006), 111–17. doi:10.1016/j.jinf.2005.03.005.
- Goswami, R, V Dadhwal, S Tejaswi, K Datta, A Paul, R N Haricharan, U Banerjee and N P Kochupillai. Species-Specific Prevalence of Vaginal Candidiasis among Patients with Diabetes Mellitus and Its Relation to Their Glycaemic Status. *The Journal of Infection* 41, no 2 (2000), 162–66. doi:10.1053/jinf.2000.0723.
- Grigoriou, Odysseas, Stavroula Baka, Evangelos Makrakis, Dimitrios Hassiakos, George Kapparos and Evangelia Kouskouni. Prevalence of Clinical Vaginal Candidiasis in a University Hospital and Possible Risk Factors. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 126, no 1 (2006), 121–25. doi:10.1016/j.ejogrb.2005.09.015.
- Grossman, Rachel and Robert Day. Sertaconazole Nitrate Rapidly Achieves High Concentrations Inthe Stratum Corneum With Prolonged Rentention Time: P1829. *Journal of the American Academy of Dermatology* 52, no 3 (2005), P128.

- Larsen, B and G R Monif. Understanding the Bacterial Flora of the Female Genital Tract. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America* 32, no 4 (2001), e69-77. doi:10.1086/318710.
- Lavery, L A, D G Armstrong, S A Vela, T L Quebedeaux and J G Fleischli. Practical Criteria for Screening Patients at High Risk for Diabetic Foot Ulceration. *Archives of Internal Medicine* 158, no 2 (1998), 157–62.
- Lewis, Ronald W, Kerstin S Fugl-Meyer, Giovanni Corona, Richard D Hayes, Edward O Laumann, Edson D Moreira, Alessandra H Rellini and Taylor Segraves. Definitions/epidemiology/risk Factors for Sexual Dysfunction. *The Journal of Sexual Medicine* 7, no 4 Pt 2 (2010), 1598–1607. doi:10.1111/j.1743-6109.2010.01778.x.
- Linhares, Iara Moreno, Paulo Cesar Giraldo and Edmund Chada Baracat. [New Findings about Vaginal Bacterial Flora]. *Revista Da Associacao Medica Brasileira (1992)* 56, no 3 (n.d.), 370–74.
- Malazy, Ozra Tabatabaei, Mamak Shariat, Ramin Heshmat, Fereshteh Majlesi, Masoumeh Alimohammadian, Nasibeh Khaleghnejad Tabari and Bagher Larijani. Vulvovaginal Candidiasis and Its Related Factors in Diabetic Women. *Taiwanese Journal of Obstetrics & Gynecology* 46, no 4 (2007), 399–404.
- Meston, C M and P F Frohlich. Update on Female Sexual Function. *Current Opinion in Urology* 11, no 6 (2001), 603–9.
- Moraes, Paula S A. Recurrent Vaginal Candidiasis and Allergic Rhinitis: A Common Association. *Annals of Allergy, Asthma & Immunology* 81, no 2 (1998), 165–69. doi:10.1016/S1081-1206(10)62804-9.
- Nowosielski, Krzysztof and Violetta Skrzypulec-Plinta. Mediators of Sexual Functions in Women with Diabetes. *The Journal of Sexual Medicine* 8, no 9 (2011), 2532–45. doi:10.1111/j.1743-6109.2011.02336.x.
- Omidvar, Shabnam, Maryam T Niaki, Fatemeh Nasiri Amiri and Farzan Kheyrkhah. Sexual Dysfunction among Women with Diabetes Mellitus in a Diabetic Center in Amol. *Journal of Natural Science, Biology, and Medicine* 4, no 2 (2013), 321–24. doi:10.4103/0976-9668.116992.
- Otero, L, V Palacio, F Carreño, F J Méndez and F Vázquez. Vulvovaginal Candidiasis in Female Sex Workers. *International Journal of STD & AIDS* 9, no 9 (1998), 526–30. doi:10.1258/0956462981922764.
- Pavlova, S I, A O Kilic, S S Kilic, J-S So, M E Nader-Macias, J A Simoes and L Tao. Genetic Diversity of Vaginal Lactobacilli from Women in Different Countries Based on 16S rRNA Gene Sequences. *Journal of Applied Microbiology* 92, no 3 (2002), 451–59.
- Peleg, Anton Y, Thilak Weerarathna, James S McCarthy and Timothy M E Davis. Common Infections in Diabetes: Pathogenesis, Management and Relationship to Glycaemic Control. *Diabetes/metabolism Research and Reviews* 23, no 1 (2007), 3–13. doi:10.1002/dmrr.682.
- Pfaller, Michael A and Deanna A Sutton. Review of in Vitro Activity of Sertaconazole Nitrate in the Treatment of Superficial Fungal Infections. *Diagnostic Microbiology and Infectious Disease* 56, no 2 (2006), 147–52. doi:10.1016/j.diagmicrobio.2006.04.006 .
- Priestley, C J, B M Jones, J Dhar and L Goodwin. What Is Normal Vaginal Flora? *Genitourinary Medicine* 73, no 1 (1997), 23–28.
- Quayle, A J. The Innate and Early Immune Response to Pathogen Challenge in the Female Genital Tract and the Pivotal Role of Epithelial Cells. *Journal of Reproductive Immunology* 57, no 1–2 (n.d.), 61–79.
- Raith, L, M Csató and A Dobozy. Decreased Candida Albicans Killing Activity of Granulocytes from Patients with Diabetes Mellitus. *Mykosen* 26, no 11 (1983), 557–64.
- Ray, Debarti, Ravinder Goswami, Uma Banerjee, Vatsla Dadhwal, Deepti Goswami, Piyali Mandal, Vishnubhatla

Sreenivas and Narayana Kochupillai. Prevalence of Candida Glabrata and Its Response to Boric Acid Vaginal Suppositories in Comparison with Oral Fluconazole in Patients with Diabetes and Vulvovaginal Candidiasis. *Diabetes Care* 30, no 2 (2007), 312–17. doi:10.2337/dc06-1469.

- Rodriguez Jovita, M, M D Collins, B Sjödén and E Falsen. Characterization of a Novel Atopobium Isolate from the Human Vagina: Description of Atopobium Vaginae Sp. Nov. *International Journal of Systematic Bacteriology* 49 Pt 4, no 4 (1999), 1573–76. doi:10.1099/00207713-49-4-1573.
- Royce, R A, T P Jackson, J M Thorp, S L Hillier, L K Rabe, L M Pastore and D A Savitz. Race/ethnicity, Vaginal Flora Patterns, and pH during Pregnancy. *Sexually Transmitted Diseases* 26, no 2 (1999), 96–102.
- Ruhnke, Markus. Epidemiology of Candida Albicans Infections and Role of Non-Candida-Albicans Yeasts. *Current Drug Targets* 7, no 4 (2006), 495–504.
- Schwebke, J R, C M Richey and H L Weiss2. Correlation of Behaviors with Microbiological Changes in Vaginal Flora. *The Journal of Infectious Diseases* 180, no 5 (1999), 1632–36. doi:10.1086/315065.
- Scudamore, J A, P J Tooley and R J Allcorn. The Treatment of Acute and Chronic Vaginal Candidosis. *The British Journal of Clinical Practice* 46, no 4 (1992), 260–63.
- Smeltzer, S. Bare, B., dir. *Brunner and Suddarth's Textbook of Medical-Surgical Nursing*. 9th Editio. Philadelphia: Lippincott, 2000.
- Smith, H L. Recurrent Candidiasis and "malcarbohydrate Metabolism". *American Journal of Obstetrics and Gynecology* 179, no 2 (1998), 557–58.
- Sobel, Jack D. Vaginitis. *New England Journal of Medicine* 337, no 26 (1997), 1896–1903. doi:10.1056/NEJM199712253372607.
- Sobel, J D. Candidal Vulvovaginitis. *Clinical Obstetrics and Gynecology* 36, no 1 (1993), 153–65.
- Sobel, J D, S Faro, R W Force, B Foxman, W J Ledger, P R Nyirjesy, B D Reed and P R Summers. Vulvovaginal Candidiasis: Epidemiologic, Diagnostic, and Therapeutic Considerations. *American Journal of Obstetrics and Gynecology* 178, no 2 (1998), 203–11.
- Sonck, C E and O Somersalo. The Yeart Flora of the Anogenital Region in Diabetic Girls. *Archives of Dermatology* 88 (1963), 846–52.
- Spinillo, A, L Carratta, G Pizzoli, G Lombardi, C Cavanna, G Michelone and S Guaschino. Recurrent Vaginal Candidiasis. Results of a Cohort Study of Sexual Transmission and Intestinal Reservoir. *The Journal of Reproductive Medicine* 37, no 4 (1992), 343–47.
- Stevens-Simon, C, J Jamison, J A McGregor and J M Douglas. Racial Variation in Vaginal pH among Healthy Sexually Active Adolescents. *Sexually Transmitted Diseases* 21, no 3 (n.d.), 168–72.
- Swidsinski, Alexander, Werner Mendling, Vera Loening-Baucke, Axel Ladhoff, Sonja Swidsinski, Laura P Hale and Herbert Lochs. Adherent Biofilms in Bacterial Vaginosis. *Obstetrics and Gynecology* 106, no 5 Pt 1 (2005), 1013–23. doi:10.1097/01.AOG.0000183594.45524.d2.
- Verhelst, Rita, Hans Verstraelen, Geert Claeys, Gerda Verschraegen, Joris Delanghe, Leen Van Simaey, Catharine De Ganck, Marleen Temmerman and Mario Vaneechoutte. Cloning of 16S rRNA Genes Amplified from Normal and Disturbed Vaginal Microflora Suggests a Strong Association between Atopobium Vaginae, Gardnerella Vaginalis and Bacterial Vaginosis. *BMC Microbiology* 4, no 1 (2004), 16. doi:10.1186/1471-2180-4-16.
- Vermitsky, John-Paul and Thomas D Edlind. Azole Resistance in Candida Glabrata: Coordinate Upregulation of Multidrug Transporters and Evidence for a Pdr1-like Transcription Factor.

Antimicrobial Agents and Chemotherapy 48, no 10 (2004), 3773–81. doi:10.1128/AAC.48.10.3773-3781.2004.

- Vylkova, Slavena, Aaron J Carman, Heather A Danhof, John R Collette, Huaijin Zhou and Michael C Lorenz. The Fungal Pathogen Candida Albicans Autoinduces Hyphal Morphogenesis by Raising Extracellular pH. *mBio* 2, no 3 (2011), e00055-11. doi:10.1128/mBio.00055-11.
- Wilson, R M and W G Reeves. Neutrophil Phagocytosis and Killing in Insulin-Dependent Diabetes. *Clinical and Experimental Immunology* 63, no 2 (1986), 478–84.
- Wilson, R M, D R Tomlinson and W G Reeves. Neutrophil Sorbitol Production Impairs Oxidative Killing in Diabetes. *Diabetic Medicine : A Journal of the British Diabetic Association* 4, no 1 (n.d.), 37–40.
- Witkin, S S. Immunology of Recurrent Vaginitis. *American Journal of Reproductive Immunology and Microbiology : AJRIM* 15, no 1 (1987), 34–37.
- Yildirim, Zuhal, Nedret Kilic and Ayse Kalkanci. Fluorometric Determination of Acid Proteinase Activity in Candida Albicans Strains from Diabetic Patients with Vulvovaginal Candidiasis. *Mycoses* 54, no 5 (2011), e463-7. doi:10.1111/j.1439-0507.2010.01951.x.
- Zhou, Xia, Stephen J Bent, Maria G Schneider, Catherine C Davis, Mohammed R Islam and Larry J Forney. Characterization of Vaginal Microbial Communities in Adult Healthy Women Using Cultivation-Independent Methods. *Microbiology (Reading, England)* 150, no Pt 8 (2004), 2565–73. doi:10.1099/mic.0.26905-0.
- Zsolt I. Sertaconazole: A Clinical Update. Proceedings of Sertaconazole International Symposium La Toja, Spain, 11–13 October 2002. Prous Science, 2002.