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Narrative Review

Estrogen on *Candida* spp. of the Vagina: Is there any effect?

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Abstract

A variety of *Candida* spp. as the most common fungus in the human body can normally be found in the vagina competing with other microbotes. Its presence is affected by variable conditions in the vaginal environment. The proliferation of *Candida* spp. in the vagina under specific conditions can result in a fungal disease known as vaginal candidiasis. More than 17 species of *Candida* out of 200 members of this genus are capable of causing diseases within the human body. Estrogen, along with other steroidal hormones, has been shown to have direct multifunctional effects on various pathogenic microorganisms by numerous activities. Its production and other factors such as disturbance of microbial balance and immune activity may alter the vaginal physical environment and promote the development of vaginal fungal infection. The vaginal functions can be affected by the level of circulation of estrogens in the blood according to the stage of the menstrual cycle in women. It also has many other functional actions on the vaginal structure. Estrogen and several other factors play an important role in determining the vaginal content of *Candida* species. Its effect could be a direct action on the cells of *Candida* or through an indirect effect on the immunity defenses of the vagina.

Keywords: *Candida*, *C. albicans*, Estrogen, Estrogen Receptor, Vagina

Introduction

Candida spp. is the most widely known fungus that lives commensally on different surfaces of the human body.[1] Over 17 species of *Candida* of 200 members of this genus are able to cause diseases in the human body.[1,2] The vagina has various and diversified species of *Candida* spp. living in the form of mycobiota.[3,4] *C. albicans* is present in more than 70% of all cases of *Candida* in the vagina.[3] The overgrowth of *Candida* spp. in the vagina under special conditions can lead to a fungal disease known as vaginal candidiasis.[5] Estrogen is one of the factors influencing the growth of *Candida* spp. in the vagina by the presence of Estrogen Receptors (ERs) in vaginal tissues.[6-8] It has been demonstrated that elevated estrogen levels increase *Candida* spp. growth in the vagina by 8.6 times.[9] This stimulation of growth by estrogens may be explained by two proposed mechanisms, the direct effect of estrogens on the growth of *Candida* spp.[10-12] and the suppression effect of estrogens on the immune status of the vagina.[13,14]

Candida spp.

Candida spp. is one of the most common types of fungi found as natural flora in various parts of the human body.[1] The genus *Candida* contains more than 200 species, which belong to the kingdom: fungi, phylum: Ascomycota, Subphylum: Ascomycotina, class: Ascomycetes, order: Saccharomycetales, and family: Saccharomycetaceae.[2] Several species of *Candida* can be found in a commensalism relationship with various surfaces of the human body, such as the skin, vagina, and other mucosal surfaces,[1] while other species live as saprophytic fungi with an inability to tolerate temperatures of 37 °C.[2] However, the pathogenic species, of which there are more than 17 species, are unable to survive outside the human body.[1]

Candida spp. as a diploid eukaryote can take different shapes, ranging from cocci, cylindrical, ovoid to elongate shape with an ability to change its shape, as other dimorphic fungi, from yeast to pseudohyphae or to true hyphae depending on the environmental conditions, such as pH or temperature, or under the effect of different compounds such as N-acetylglucosamine or proline.[2,15] It usually lacks a sexual stage and some species were reclassified with a different name, such as change of *Torulopsis glabrata* into *Candida glabrata*.[2] The cell wall of *Candida* spp. is mainly composed of

structural polysaccharides such as mannans, glucans and a small amount of chitin.[2]

Colonization of *Candida* spp. on human surfaces can facilitate it to becoming an opportunistic fungal pathogen under specific conditions which mostly relate to the immune system.[15] Most people have at least one species of *Candida* living on their body surface.[1] Overgrowth and colonization of *Candida* spp. on any human surface will lead to fungal infection called candidiasis or candidosis, which is infrequent in healthy individuals.[1,2,15] This colonization usually takes a biofilm structure that is an important factor in the *Candida* infection.[1] The severity of candidiasis can vary from harmless as with mucocutaneous infection or life threatening systemic infection depending on the strain virulence, site of infection and the immune state of the human.[1,16] Morbidity and mortality due to candidiasis are recorded worldwide, especially in patients with a critical illness.[1]

Hyphae is considered as the infectious stage of *Candida* spp.[2] This has been supported by four mechanisms: the first is that hyphae has a mechanical force to invade or penetrate epithelial layers; the second is that hyphae has an ability to destroy endothelial cells; the third illustrates an ability of hyphae to grow inside phagocytosic cell and to lyse or destroy this cell; and the fourth depends on the hyphal production of thigmotropism as a contact sensing factor to help its penetration through a small area or groove in the host tissue.[17] Pathogenesis of *Candida* spp. can also occur by the presence of variable virulence factors such as secretion of hydrolytic enzymes (e.g. proteases, phospholipases and haemolysins) and other associated molecules with adherence to host tissue and biofilm formation.[1] Transition of *Candida* spp. from yeast to hyphae is another virulence factor that should be considered.[17]

C. albicans is the most common pathogenic species causing candidiasis, followed by *C. glabrata, C. parapsilosis, C. krusei, C. tropicalis* and *C. kefyr*.[2,15,16] These species including *C. albicans* have been responsible for causing more than 90% of candidiasis.[3,18] Recently, non-albicans *Candida* species (NAC) have been recorded to cause higher rates of candidiasis with similar clinical features as *C. albicans*.[16,18]

Candida spp. in the Vagina

Candida spp. is normally found on the vaginal surface layers as part of vaginal mycobiota.[3,4] From the 196 fungal Operational Taxonomic Units (OTUs) of the vaginal origin, 16 OTUs were related to *Candida* spp.[19] Classes of Ascomycetes and Basidiomycetes and genera of *Candida* and *Saccharomyces* are the most predominant fungi in the vagina.[20] The oomycetes fungal class could also be added to previous classes as found in women with recurrent vaginal candidiasis or with allergic rhinitis.[21]

C. albicans represents more than 70% of all species of *Candida* in the vagina, while the presence of NAC are variable based on population studied, geography, and culture methods.[3] Among pregnant women in Saudi Arabia, *C. albicans* represented 70.2% of total isolates from the vagina, followed by five other species.[22] Other studies found that the prevalence of *C. albicans* in vagina of healthy women is about 67.6%.[19] while it represented 26.3% in both of healthy and pregnant diabetic women, followed by *C. glabrata, C. tropicalis, C. krusei, C. parapsilosis*, and *Saccharomyces cerevisiae*.[20] From the vagina of 34 asymptomatic adolescent women, *C. albicans* was found in 91%, while there were only two isolates of *C. glabrata* and one of *C. tropicalis*.[23] Beigi *et al.* (2004) also found that the majority of healthy women (98%) were colonized with *C. albicans*, while other species colonized in only 2% of women tested.[24]

The growth of *Candida* spp. on the vaginal surface is usually controlled by the activity of other microorganisms, especially *Lactobacillus* spp. which are always in competition with fungi to adhere to epithelial layers and prevent the overgrowth of yeast through the production of organic acids (e.g. lactic acid) which lower vaginal pH.[25,26] Thus, increased colonization of *Candida* spp. on the vaginal surface under specific conditions will turn this yeast into a pathogenic organism causing vaginal candidiasis.[4,27] Vaginal candidiasis could be the most prevalent type of candidiasis in women with high rates of recurrent infection.[5] From the result of a cohort study, including 1248 asymptomatic young women for one year, about 70% were diagnosed to have colonization of *Candida* spp. after 1-2 visits (each visit after four months) and 4% after four visits, while 30% were never colonized by yeast during the study period.[24]

Most colonization by vaginal *Candida* spp. has shown no or few symptoms and can be stimulated by many factors such as sexual activity, diabetes, use of birth control or contraceptives, smoking, alcoholism,

and drug addiction.[23,24,28,29] Women at middle age are also at risk of overgrowth of *Candida* spp.[29] On the other hand, growth of *Candida* spp. has been found not to be affected by many associated factors such as bacterial vaginosis, local immunomodulators, and periods of antifungal usage.[23,24] However, many symptoms can be recognized in women with vaginal overgrowing yeast, including pruritus, increased discharge, dysuria, malodor, and burning with focus on two of them; vulvovaginal burning and pruritus.[24,27,30] For diagnosis of vaginal colonization by *Candida*, clinical signs and symptoms are usually not enough and laboratory tests are needed for confirmation.[30,31]

Effects of Estrogen on the Vagina

Estrogen is an important type of sex hormone in a women's body through its regulatory activity of the reproductive system and breast development.[32,33] It is usually metabolized in the human body into three types: estrone (E1), 17β-estradiol (E2), and estriol (E3).[34,35] The activities of estrogen are performed by interaction with specific protein receptors called estrogen receptors (ERs).[36,37]

The vagina can be affected by the circulating level of estrogen in the blood depending on the stage of the menstrual cycle in women. Decreasing levels of estrogen during the elderly age of women will lead to a decline of its level in the vagina, which will affect the maturation of vaginal tissues.[6] The presence of ER in the vagina makes it affected by varied activities of estrogen.[6-8] Both of ERα and ERβ are found on the vaginal stroma and epithelial surface.[38] Basal, parabasal, and intermediate cell layers are the most enriched areas with ER in vaginal epithelium tissues, while its location in stroma is mostly found in the vaginal lamina propria.[39,40] The concentrations of ER in the vagina range between a low level of 4 fmol/mg protein (1 fmol = 10^{-15} mole) and a high level of 119 fmol/mg protein.[41] These concentrations are mostly affected by the location of the ER and the period of menstrual cycle and not by the level of estrogen in the circulatory system.[8,41] However, the concentration of the ER in both premenopausal and postmenopausal women are varied from low and high. Wiegerinck *et al.* (1980) found that ER was higher in postmenopausal women (4 to 119 fmol/mg) and lower in premenopausal women (12 and 91 fmol/mg),[41] while Carlo *et al.* (1985) found insignificant differences in the ER level between those two reproductive sexual stages (10-83 fmoles/mg in postmenopausal and 12-78 fmoles/mg in premenopausal women).[8] Expression of ERα was reduced in vaginal mucosa and stroma of the postmenopause period in comparison with that in premenopausal women, while ERβ expression reduced in the mucosa of postmenopausal women compared with those in the premenopausal period.[38]

In addition to its effect on normal activities of the vagina, estrogen has many other functional actions on the vaginal structure such as increasing glycogen and control of enzyme activities, such as nitric oxide synthase and arginase in distal vaginal tissues.[6,7,42] Increased glycogen in vaginal tissue will enhance the growth the bacteria *Lactobacillus* spp. and its production of acid responsible for an acidic environment with low pH (3.5-4.5).[6,7] Keratinization of vaginal epithelial tissues to cornify shape, thicken and slough is another effect of estrogen on the vaginal structure.[27]

A significant decrease in estrogen level will produce an undesirable condition in the vagina.[7] Vaginal or Vulvovaginal Atrophy (VVA) is a common disorder resulting from a deficiency in estrogen level, especially during the postmenopausal period.[6,7,43,44] In two studies, it developed in 10-40% or in 36-90% of postmenopausal women.[43,44] This atrophy is characterized by many signs or symptoms in the vagina, including dryness, itching, thinning of vaginal layers, decreased pH, loss of pelvic support, decreased tissue elasticity, painful sexual intercourse, and bleeding.[6,43-45] However, treatment with a local low dose of estrogen (estriol) will relieve these symptoms and return normal structure and function of vaginal tissues.[43]

Effects of Estrogen on Vaginal *Candida* spp.

Estrogen, as well as other steroid hormones, has been proven to have direct multifunctional effects on various pathogenic microorganisms through many activities, including regulation of microbial replication, colonization, biofilm formation and adhesion to host surfaces.[46] Its production and other factors such as disturbance of microbial balance, and immune activity can change the vaginal physical environment and encourage the development of vagina fungal infection.[27] A variety of *Candida* spp., especially *C. albicans*, can bind to estrogen through its content of a specific binding protein called Estrogen Binding Protein (EBP1).[47,48] EBP1 is mainly located in the nucleus of

C. albicans and not in the cytoplasm.[49] Thus, *Candida* spp. has shown *in vitro* and *in vivo* sensitivity to estrogen with a concentration- depended manner.[9] In general, increasing estrogen level has an important role for the development of vaginal candidiasis.[50]

Several studies have shown that the growth or colonization of *C. albicans* in the vagina can increase in the presence of estrogen. This stimulation of growth could be increased to 8.6-fold in the vagina due to the effect of estradiol.[9] *C. albicans* was found to survive and remain vital in the vagina of rats for up to 10 days after treatment with estradiol cypionate compared with the untreated group.[12] Adhesion of *C. albicans* on the vaginal epithelial tissue can also increase in the presence of estradiol or estriol with varying degrees.[51]

Encouragement of estrogen to vaginal infection with *Candida* spp. can be explained by two mechanisms. The first is that estrogen has a direct effect on *Candida* spp. to grow faster through its content of ERP1.[10-12] 17β -estradiol and ethynyl estradiol at concentrations 10^{-5} to 10^{-10} M increased the formation of germ tubes by *C. albicans* through their effect on increased expression of *CDR1* and *CDR2* genes, while this effect was low in the presence of 17α - estradiol or estriol.[10] White and Larsen (1997) also showed that beta estradiol at 100 times lower than 1 μM increasing stimulation of clinical isolates of *C. albicans* to germinate and change morphology.[11] A concentration-dependent antifungal effect of 17β-estradiol against *C. albicans* was also demonstrated by Essmann and Larsen (2000) when growth of *C. albicans* was promoted at a low concentration (1×10^{-9} M) of 17β-estradiol, while it was suppressed at a high concentration (1×10^{-6} M).[12] On the other hand, Kent (2016) found no significant *in vitro* effect of 17β-estradiol on the growth of *C. albicans* at concentrations ranging from 0.1 nM to 1 μM.[14] Differences in *Candida* strain could also affect the response of this fungus to estrogen, as shown when the 17β-estradiol isomer promoted the growth of one strain from 30 strains of *C. albicans* to form more biomass in culture media than the 17α-estradiol isomer.[52] Also, 17β-estradiol at 10 μg/ml proved to show an inhibitory effect on hyphae forming during morphological transition of *C. albicans*.[47]

The second mechanism whereby estrogen promotes the growth of *Candida* spp. depends on the effect of estrogen to inhibit or attenuate defensive immunity in the vagina.[13,14,53] Based on experiments in mice, the inhibitory effect of vaginal epithelial cells against the growth of *C. albicans* reduced in the presence of estrogen. Furthermore, any decrease in the level of estrogen will encourage *C. albicans* to cause vaginal infection.[13] Another study in female mice showed that the secretion of immunity factors such as TNF-α in the vagina was also inhibited by estradiol after 2 and 4 hours challenge with *C. albicans*.[14] *Lactobacillus* spp. in the vagina also enhance 17β-estradiol reduction of vaginal immunity against *C. albicans* by suppressing expression of genes related to the immune system such as NF-κB-related inflammatory genes.[53] Thus, the increasing activity of this bacterium under the effect of low estrogen level could reduce the growth of *Candida* spp. in the vagina.[54] Restriction of neutrophils at the apical epithelial layer of the vagina and prevention of their transfer into the vaginal lumen by the effect of estradiol on CD44 and CD47 epithelial expression was shown to stimulate the growth of *C. albicans* in the vagina.[55]

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Conflict of Interest

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