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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 fungi in the human body can normally be found in the vagina competing with other microbotes. Their presence is influenced by a variety of 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 as well as 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.

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Introduction

Candida spp. are the most widely known fungi that live commensally on different surfaces of the human body (1). Over 17 species of Candida of 200 members of this genus are able to cause disease 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). The effect of estrogens on the vagina and its species content of Candida were discussed in this review.

Literature review

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 belonging to the kingdom: fungi, phylum: Ascomycota, Subphylum: Ascomycotina, class: Ascomycetes, order: Saccha-

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romycetales, 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 a 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 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 as an important factor in 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 critical illness (1).

Hyphae is considered 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 included C. albicans have been responsible for causing more than 90% of candidiasis (3,18). Recently, non-albicans Candida species (NAC) have been recorded as causing higher rates of candidiasis with similar clinical features as C. albicans (16, 18).

Candida spp. in the vagina

Candida spp. can normally found on the vaginal surface layers as part of vaginal mycobiota (3-4). From 196 fungal operational taxonomic units (OTUs) of 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). 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). 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 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 rate 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 4 months) and 4% after 4 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 decline of its level in the vagina after it was higher in the premenopausalstage, 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)(Fig 1). 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 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 of premenopausal and postmenopausal women can 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 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 stroma only 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 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 vaginal structure (27)(Fig 1).

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) (Fig 1). 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 local low dose of estrogen (estriol) will relieve these symptoms and return normal structure and function of vaginal tissues (43).

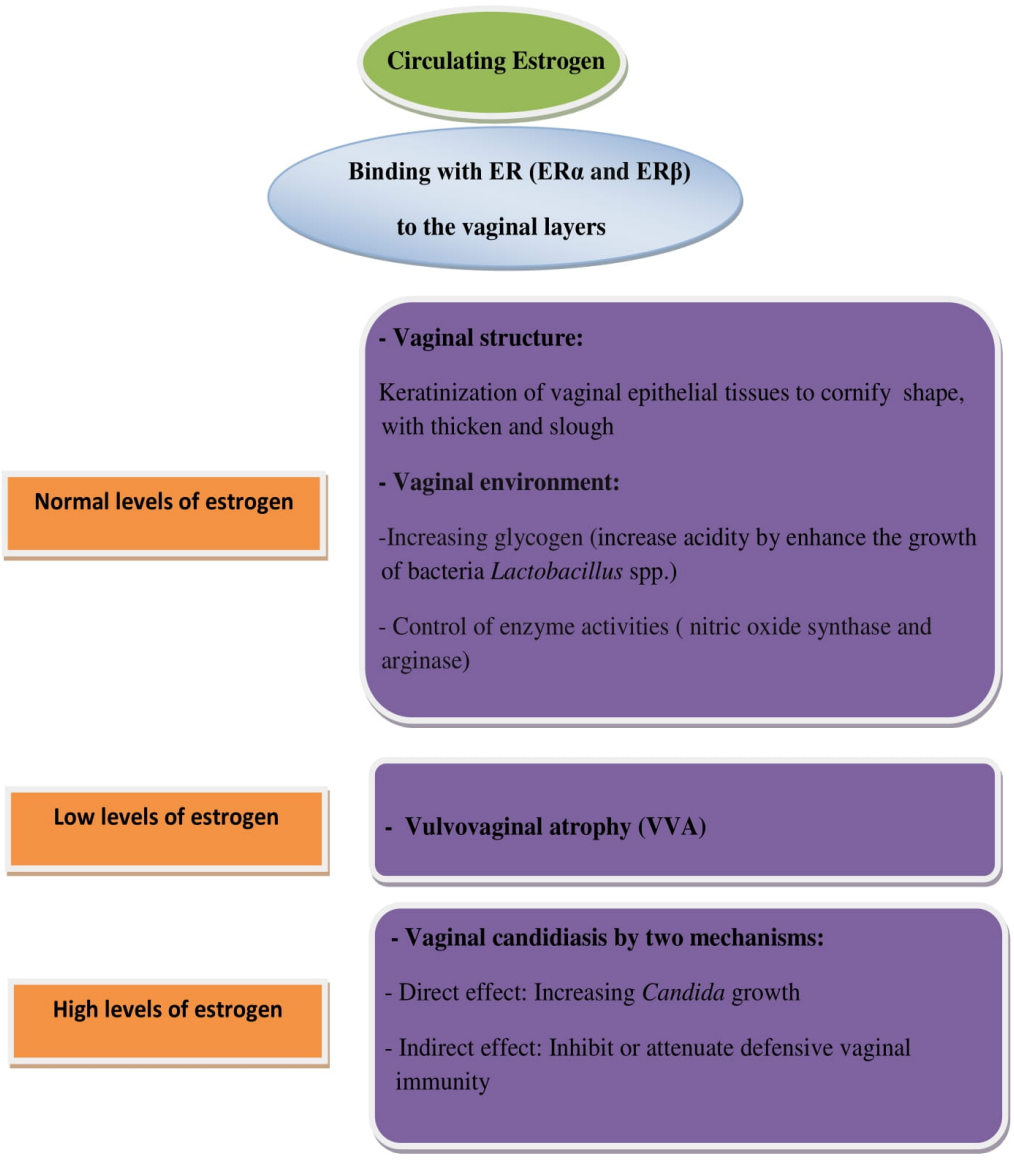

Figure 1: Effect of estrogen on the vagina and its content of *Candida* spp.

Figure 1: Effect of estrogen on the vagina and its content of Candida spp

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 encourage role for development of vaginal candidiasis (50) (Fig 1). This increase occurs primarily after the use of hormone replacement therapy (HRT) which can considerably alter the normal vaginal flora (51).

Thus, increasing estrogen levels through HRT has a role in promoting the development of VVC and making antifungal treatment unsuccessful for this type of fungal infection (52). Several studies showed 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 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 rat 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 (53).

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 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 low concentration (1× 10–9 M) of 17β-estradiol, while it was suppressed at 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 0.1nM to 1μM (14).

Differences in Candida strain could be also affect the response of this fungus to estrogen, as shown when the 17β-estradiol isomer promoted growth of one strain from 30 strains of C. albicans to form more biomass in culture media than the 17α-estradiol isomer (54). 17β-estradiol at 10 μg/ml also 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 (13-14,55).

Based on experiments in mice, inhibitory effect of vaginal epithelial cells against the growth of C. albicans was found reduced in the presence of estrogen and any decrease in estrogen level will encourage C. albicans to cause vaginal infection (13). Another study in female mice showed that 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 have a role to 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 (55). Thus, increasing activity of this bacterium under the effect of low estrogen level could reduce the growth of Candida spp. in the vagina [51]. 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 growth of C. albicans in the vagina (56).

In conclusion; the harmony of Candida colonization with other vaginal flora can be disrupted by numerous external and internal factors. Estrogen as one of the important sex hormones in the woman's body has many structural and physiologic effects on the vagina. These effects may include an increase or decrease in density of Candida vaginal species. Generally, increasing estrogen levels usually promotes the growth of Candida spp. and the

development of VVC either by effects on the vaginal environment or directly on Candida.

Conclusion

The harmony of Candida colonization with other vaginal flora can be disrupted by numerous external and internal factors. Estrogen as one of the important sex hormones in the woman's body has many structural and physiologic effects on the vagina. These effects may include an increase or decrease in density of Candida vaginal species. Generally, increasing estrogen levels usually promotes the growth of Candida spp. and the development of VVC either by effects on the vaginal environment or directly on Candida.

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Conflict of interest

The authors declare no conflicts of interest.

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