Ministry of Higher Education and Scientific Research
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College of Science
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The synergistic effect of *Candida* sp. and vaginal bacterial (BV) infection on infertility: mini review

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By
IsraaQtayba Ahmed, Alaa Ali Abdullah

Fatima AbdAlmonem, GeylanMuqdad Karim, and

FotonFadil Ahmed

Supervised by
Dr.AlyaaMaanAbdelhameed

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بسم الله الرحمن الرحيم

{قال الذي عنده علم من الكتاب أنا آتيك به قبل أن يرتد إليك طرفك فلما رآه مستقراً عنده قال هذا من فضل ربي ليبلوني أأشكر أم أكفر ومن شكر فإنما يشكر لنفسه ومن كفر فإن ربي غني كريم}.

صدق الله العظيم
سورة.....النمل(الاية ...٤٠..)

الاهداء

إلى من ألفيتُ حبهُ مطبوعاً على شغاف قلبي والدي الحنون

إلى أُمي لحنُ حنين خالد، وربيع قلبي ونور صدري وجلاء حزني أُهديكم أيقونةَ رحلتي العلمية.

إلى من كانوا ملاذي و ملجئي وَ مَصَادري و خزائن المعلومات يامن تذوقت معهم أجمل اللحضات إلى من سأفتقدهم ، واتمنى أن يفتقدوني اساتذتي الأجلاء

الشكر والتقدير

الحمد لله رب العالمين والصلاة والسلام على أشرف الأنبياء والمرسلين سيدنا محمد وعلى آله وصحبه ومن تبعهم بإحسان إلى يوم الدين...

وأما بعد..
فإننا نشكر الله تعالى على فضله حيث من علينا بإنجاز هذا العمل بفضله، فله الحمد أولاً و آخراً...

ثم نشكر أولئك الأخيار الذين مدوا لنا يد المساعدة، خلال هذه الفترة...
و في مقدمتهم أستاذنا المشرف على البحث الدكتورة علياء معن عبد الحميد و قسم التقانة الاحيائية الذي لم يدخر جهداً في مساعدتنا و تذليل العقبات التي واجهتنا أثناء عملنا لإنجاز بحثنا المتواضع هذا..

وأخيراً وليس آخر

لا يسعنا إلى أن نتقدم بمنتهى الشكر والتقدير إلى والدينا الأعزاء و جميع الأخوة و الأصدقاء الذين كانوا لنا خير سند وعون بعد المولى القدير طوال مسيرتنا الدراسية نحو العلم و المعرفة.

اقرار المشرف وترشيح رئاسة قسم التقانة الاحيائية

اقر بان اعداد هذا البحث الموسوم بـ

Candida infection and Bacterial vaginosis in infertility women

الذي قدمته الطالبات/الطلبة (اسراء قتيبة احمد، الاء علي عبد الله، فتون فاضل احمد،فاطمة عبدالمنعم هندي ، جيلان مقداد كريم) قد جرى تحت اشرافي في كلية العلوم/قسم التقانة الاحيائية/جامعة ديالى، وهو جزء من متطلبات نيل درجة البكالوريوس في علوم التقانة الاحيائية.

التوقيع:
الاسم: علياء معن عبد الحميد
المرتبة العلمية: استاذ مساعد دكتور

قسم التقانة الاحيائية/كلية العلوم
التاريخ: / ٧ /٢٠٢٠

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الاسم:
رئيس قسم التقانة الاحيائية
كلية العلوم/جامعة ديالى
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نشهد باننا اعضاء لجنة المناقشة، اطلعنا على هذا البحث الموسوم بـ

Candida infection and Bacterial vaginosis in infertility women

الذي قدمه كلا من الطالبات (اسراء قتيبة احمد، الاء علي عبدالله، فاطمة عبدالمنعم هندي ، جيلان مقداد كريم، فتون فاضل احمد) في محتوياته وفيما لها علاقة به، ونعتقد بانهم جديرون بالقبول لنيل درجة البكالوريوس في علوم التقانة الاحيائية بتقدير( ).

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Abstract

Bacterial vaginosis (BV) can have a prefund impact on the health of woman and their neonates. Woman with BV have complex communities of bacteria such as ***Staphylococcus epidermidis, Streptococcus*** sp. Healthy women are always colonized with *Lactobacillus*. However, vaginal candidiasis affects 75% of all women at least once during their life and *Candida albicans* has been implicated in infertility. Change in the vaginal microbiota have been associated with several adverse health outcomes including premature birth and pelvic inflammatory diseases. In vitro studies also show that *Candida albicans* influences spermatozoa quality suggesting an impact on male factor infertility. However, few studies have investigated bacterial and *Candida* diversity impact on infertility. Most women who reported Epidemiology of vulvovaginitis candidiasis and recurrent (VVC /RVVC) were simultaneously colonized in both the oral vaginal sites with the same Diploid strain type (DST). DSTs were participant specific, and occasional intra-strain diversity for individuals were observed. Pronounced genetic diversity was detected in couples undergoing anti-fungal treatment. Differences in immune response based on participant sex rather than fertility status was observed. The microbiology of BV is heterogeneous. The presence of *Candida* species coating the vaginal epithelium in some subjects with BV suggests that biofilms may contribute to this condition. This review outlines selected aspects in the current understanding of BV and *C. albicans* pathogenesis and interactions with the host, and present several antibiotics, tools developed in the postgenomic era to study these topics.

Keywords:
Infertility, *Candida albicans*, Biofilm formation, Candidiasis Vaginal, resistance to antifungal.

Contents

Abbreviating	Meaning
WHO	World Health organization
CDC	The Centers for Disease control
BV	Bacterial vaginitis
STI	Sexually transmitted infection
VVC	Vulvovaginitis Candidiasis
RVVC	Recurrent VVC
Saps	Secreted aspartyl Protienases
PI	Phospholipases
PIA	Phospholipases A
PIB	Phospholipases B
PID	Phospholipases D
PIB1	Phospholipases B1
PIB2	Phospholipases B2
RHOE	Reconstituted human vaginal epithelium
Sap	Secreted aspartyl Protien
NIH	National Institutes Health
ALS	Agglutination -like sequence gene
PAMP	Pathogen Associated molecular pattern
GPd2	A glycerol-3 phosphate dehydrogenase
CDR1	Candida Drug Resistance Protien 1
CDR2	Candida Drug Resistance Protien 2
AMP	Amphotercin B
5-FC	5- Flocytosine
5-Fu	5- Fluorouracil
UPRTase	Uracil phosphoribosyl transferase

1. Literature Review

1.1 Infertility

The World Health Organization (WHO) has documented infertility as a public health issue worldwide. Based on WHO criteria, infertility is defined as failure toachieve conception after 12 months or more of regular unprotected sexual intercourse (Boivin et al., 2007). Infertility is classified as primary for a couple with no children, or as secondary after having one child.

Based on a systematic review, the global estimate of infertility for non-surgically-sterilized fertile women revealed a regional variation in infertility with a global estimation of 72.4 million infertile women worldwide, of whom 40.5 million are seeking fertility treatment. Moreover, estimation of the infertility based on 277 surveillance representing 190 different region, revealed 48.5 million couples worldwide were unable to have a child after five years (Mascarenhas et al., 2012). An epidemiological study of infertility in Scotland revealed that approximately one in five women had experienced infertility (Thrower and Bhattacharya, 2009), and the authors concluded that the main factors associated with infertility were endometriosis, *Chlamydia trachomatis* infection and pelvic surgery. Moreover, the prevalence of infertility was estimated at 2.5% in the UK. A subsequent study in 2009 estimated annual infertility at 0.9 among 1000 couples. The latest estimated infertility rate in the UK is one in seven couples (Fertilisation and Authority, 2011).

The epidemiology of infertility is based on those infertile couples who seek help. Basically, the main overall causes of female infertility are ovulatory disorders, with an incidence ranging between 21–32%, and tubal disorders which vary between 14–26% (Thonneau et al., 1991). Importantly, the relationship between the presence of pathogenic microorganisms in the reproductive tract and infertility is widely documented.

1.2 Female genital infection and infertility

Common components of the vaginal microbial community found in healthy women are the anaerobic bacteria *Staphylococcus epidermidis*, *Streptococcus*sp.,*Lactobacillus* and occasionally the fungus *Candida*(Bao et al., 2018).

Microflora colonisation can extend to colonisation of internal organs such as the female uterine cavity, which was thought to be a sterile organ .*Lactobacillus* is an obligate hetero-fermenter, utilising glucose obtained from epithelial vaginal cells to produce lacticVaginitis has a significant impact on the female reproductive tract, due to the subsequent inflammatory response (hormonal, cell-mediated) in accessory organs that can cause a total blockage of the fallopian tubes.(Fiore et al., 2008). Untreated low-level infection leads to pelvic inflammatory disease, which results in chronic pelvic pain, and can cause ectopic pregnancy which contributes to infertility. The Centers for Disease Control and Prevention (CDC) in the USA recommended the importance of screening for infection in all sexually-active females under 25 years of age (Smirnova et al., 2009). In this context, thirty healthy pregnant women and forty women of a similar age with secondary infertility were subjected to screening for the presence and previous infection incidence with *Chlamydia trachomatis*. The results indicated that the prevalence of past chlamydial infection is highly statistically significant in women with secondary infertility . In terms of bacterial vaginitis (BV), an increase in pro-inflammatory

cytokines such as interleukin (IL)-6 and IL-8 is used as an indicator of BV(Tachedjian et al., 2017). Although infertility has been associated with BV infection, the impact of fungal infection such as with *Candida* is unclear. This could be as a result of lack of study, the selection criteria used or missed diagnosis of *Candida*.

1.3Bacterial vaginitis (BV)

BV is the commonest cause of abnormal vaginal discharge in woman of childbearing age but may also be encountered in perimenopausal women(Donders, 2010). In Caucasian women the prevalence is 5–15%; in Black women it is higher at 45–55%. Women who have sex with women (WSW) share similar *Lactobacillary* types, are more likely to have concordant vaginal microbiota (flora) patterns, and are at increased risk for B.V.

BV has been reported to be three times more prevalent among infertile than in fertile women and is associated with a two-fold elevated risk of preclinical pregnancy loss following in vitro fertilization-embryo transfer (Shannon, 2018).

Bacterial vaginosis may also facilitate the transmission of other sexually transmitted bacteria such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*(Unemo et al., 2017). There have also been reports linking BV to laparoscopy-confirmed salpingitis and with infertility due to fallopian tube occlusion. A BV diagnosis has also been associated with spontaneous abortion, low birthweight, increased neonatal morbidity(Svare et al., 2006), and higher rates of postpartum endometritis (Table 1). However, the associations between BV and adverse pregnancy outcomes are mostly derived from inadequately designed studies that did not fully evaluate other causes of pregnancy-related pathology. BV can arise and remit spontaneously and although not strictly considered a sexually transmitted infection(STI) it is associated with sexual activity.

Table 1: Prevalence of BV and abnormal vaginal microflora in women with infertility.

Study name	Origin of study	BV prevalence	Prevalence of all abnormal microflora
McCaffrey *et al*. (1997)	Dublin, Ireland	10.0% (12/120)	25.0% (30/120)
Morgan *et al*. (1997)	London, UK	18.5% (37/199)	24.0% (48/199)
Ralph *et al*. (1999)	Leeds, UK	24.6% (190/771)	36.0% (278/771)
Liversedge *et al*. (1999)	Bristol, UK	25.6% (77/301)	39.6% (119/301)
Gaudoin *et al*. (1999)	Glasgow, UK	16.3% (40/246)	—
Spandorfer *et al*. (2001)	New York, NY, USA	4.2% (14/331)	19.3% (64/331)
Wilson *et al*. (2002)	Leeds, UK	24.3% (182/749)	36.4% (273/749)

Eckert *et al*. (2003)	Seattle, WA, USA	11.0% (10/91)	45.0% (41/91)
AboulEnien *et al*. (2005)	Alexandria, Egypt	25.0% (10/40)	—
Mania-Pramanik *et al*. (2009)	Mumbai, India	25.9% (29/112)	—
Boomsma *et al*. (2010)	Utrecht, The Netherlands	8.6% (17/198)	30.3% (60/198)
Selim *et al*. (2011)	Ismailia, Egypt	36.6% (26/71)	83.1% (59/71)

(van Oostrum et al., 2013)

1.4 Candidiasis

Candida spp are usually benign fungi on the skin and mucosae of many humans. If an individual is immunocompromised *Candida*, in particular *C. albicans*, which is the most common fungal pathogen in humans, can enter the bloodstream and cause a life-threatening systemic infection. *Candida* is perfectly adapted to adhere to host tissues, pass though epithelia and endothelia, invade virtually every organ and escape the immune response of the host . They normally pose no threat because they are kept under control by other microorganisms, innate immune responses of the host and an epithelial barrier. However, under certain circumstances, for example when patients are immunocompromised, *Candida* can become a pathogen (Tang et al., 2016). Risk factors include immunesupressive therapy, chemotherapy-induced neutropenia, and elimination of competing microorganisms by prolonged treatment with broad-spectrum antibiotics, indwelling vascular catheters, abdominal surgery and long-term hospitalization. *Candida* can cause diseases that range from superficial infections, that can affect the vaginal and oral mucosae, to systemic infections. An estimated 75% of all women are affected by vulvovaginal candidiasis at least once in their lifetime (Gonçalves et al., 2016).

Around 5–10% of these women experience recurrent *Candida* vulvovaginitis. Of the around 150 *Candida* species, that have been identified, more than 17 can cause invasive candidiasis.

Identification of *Candida*

Identification of the *Candida* species involved is an essential step for VVC management to provide insight into the degree of virulence of the species and of antifungal susceptibility profiles. There are approximately 300 fungal species which have been recognized as potential human pathogenic agents, however, the most commonly-encountered in the clinical setting is *Candida* with *C. albicans* being the predominant species encountered in clinical samples. New improved identification tools will resolve many misidentifications and reveal the emergence of species that have been previously misidentified.

Candida isolates can be distinguished by culture in selective medium (Odds and Bernaerts, 1994). Different chromogenic media have been developed and made available for *Candida* isolation and identification. These media facilitate differentiation based on colony colour as a result of the cleavage of chromogenic substrates by species-specific enzymes (Váradi et al., 2017). The germ-tube test is a rapid identification method for *C. albica*ns that can be accomplished in 2–4 h; however, it does not always give accurate results, since approximately

5% of *C. albicans* isolates have been reported to not produce a germ tube , while some *C. tropicalis* isolates also exhibit germ-tube formation . The differentiation between *C. dubliniensis* and *C. albicans* is theoretically possible based on the use of growth media containing a high concentration of NaCl and also by high temperature based on the formation of *chlamydospores*; however such a method could be time consuming for clinical practice. Tests involving the assimilation or fermentation of sugars can take 18–72 h for complete identification.

Epidemiology of vulvovaginitis Candidiasis(VVC) and recurrent VVC (RVVC)

Vulvovaginitis *Candidiasis* (VVC) is defined as an acute inflammatory reaction in the absence of other infectious aetiology. VVC is sometimes associated with clinical signs and symptoms including intense pruritus, vaginal discharge, as an infection requiring treatment (Odds and Bernaerts, 1994). In one study, *C. albicans* was associated with symptoms of VVC, while the presence of non-*C. albicans* yeasts was associated with asymptomatic women. However, there was no association between the number of fungal colonies and the presence of symptoms. Some studies have reported an increasing trend in the occurrence of non-albicans species (Playford et al., 2010).It is widely distributed in some geographical areas and is reported to constitute 1.5% of *Candida* isolated from RVVC Chinese patient (Hasanvand et al., 2017). Typically, a single species is identified in cases of VVC; however, between 1-10% of VVC incidence is associated with the isolation of two or more species from the same vaginal culture. Most of these mixed infections are because of association between *C. albicans and C. glabrata.*

1.5Alternative management of RVVC:

Complete relief of candidiasis cannot be established and remains elusive; therefore ,identification of alternative therapies is crucial. However, the two most promising strategies that have attracted attention are Probiotics and the development of a vaccine.

Probiotics

The beneficial effects of probiotics have been suggested based on observational and cross-over studies.RVVC has been associated with lower baseline numbers of *Lactobacillus* or the absence of *Lactobacillus* producing H_2O_2(Vladareanu et al., 2018).A three-fold reduction in episodes of RVVC was found for women who consumed yogurt containing *Lactobacillus acidophillus* compared to those who did not(Hilton et al., 1992). *In vitro* investigation of the effects of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 on *C. albicans*, revealed both loss of metabolic activity and increased mortality of C.*albicans*. Moreover, transcriptome analyses revealed increased expression of stress-related genes and lower expression of genes involved in fluconazole resistance. Although some clinical trialshave demonstrated the effectiveness of *Lactobacillus rhamnosus*GR-1 and *Lactobacillus fermentum*RC-14, administered either orally or intravaginally, in improving clinical symptoms and providing longer relief without recurrence (Hilton et al., 1995, Williams et al., 2001, Reid et al., 2003),the results of other trials did not support this conclusion (Shalev et al., 1996,

Salminen et al., 2002).However, this approach remains promising for complicated cases in women with a genetic predisposition.

1.6 Pathogenicity Mechanisms

Most *Candida* infections originate either from epithelia or from biofilms present on indwelling medical devices. It seems that most systemic infections arise from the gastrointestinal tract which is the largest reservoir of *C. albicans* . For dissemination, cells pass the epithelial barrier and traverse the endothelium. Cells then spread via the bloodstream and exit by passing through the endothelium again. Finally, cells can invade virtually every internal organ. Cells can also gain access to the bloodstream from the epidermis through severe burns, from the gastrointestinal tract by damage through surgery, or via contaminated central venous catheters(Höfs et al., 2016). *Candida* is perfectly adapted to survive in a wide range of host niches and to evade the immune system. It has to cope with extreme or rapidly changing environmental conditions. A number of strategies and attributes explain why *Candida* is such a successful pathogen Important factors include adhesion, secretion of hydrolases, polymorphism, formation of biofilms, metabolic flexibility and adaptation to stress .Most research has been done with *C. albicans*, and to a lesser extent with *C. glabrata* .Comparatively little is known about other *Candida* species.

Extracellular hydrolytic enzyme

Several hydrolytic enzymes are secreted by *Candida* species and play roles in adhesion ,invasion and destruction. Secreted aspartyl proteinases (Saps), phospholipases, lipases and haemolysins are important enzymes that have been implicated in *Candida* species pathogenicity.

Phospholipase

The secretion of extracellular phospholipases are ahetero-genus group of hydrolytic enzymes that 2y

Proteinase

Aspartyl proteinases are encoded by 10 SAP genes in *C. albicans* .This family islessextensivein other *Candida* species, with three SAP genes identified in *C. parapsilosis*, and at least four in *C. tropicalis*(Odds, 2008, Merkerová et al., 2006, Zaugg et al., 2001);the remaining species are still not characterized. The restriction of proteinase families to only the most pathogenic *Candida* spp. is suggestive of the possible roles and functions of these enzymes in fungal pathogenicity. All proteinases hydrolyse peptide bonds (CO–NH) in proteins(Barrett and Rawlings, 1991). This suggests that the function of proteinases is nutrient acquisition through degradation of complex proteins to peptides for cell uptake and utilization. However,SAP2 proteinases areable to digest a variety of protein types found in mucosal surfaces. It was thought that SAP secretion would contribute to evasion from the host immune system by degrading

IgA and intracellular lysosomal enzymes of leukocytes(Naglik and Hube, 2010).Further it has been found that Sap2 can activate 1ILB which contributes to the continuous inflammationof host sites that eventually contribute to the persistence of *Candida* colonization(Naglik et al., 2003a).However, different expression level shave been recorded based on different anatomical sites. For example *SAP1, SAP3,*and*SAP6–SAP8*expression iscorrelated with vaginal disease with*SAP1, SAP3,*and*SAP8*preferentially expressed in vaginal, rather than oral, infections (Naglik et al., 2003b).

Biofilmformation

Typically, biofilms are defined as planktonic and surface-attached multicellular communities attached one to another, enclosed within a self-produced protective extracellular matrix, and can be considered to form complex communities of microbes that cooperatively interact.
The National Institutes of Health (NIH) estimated that 65–80% of human microbial infections are the result of microbial biofilms (Donlan, 2002, Lohse et al., 2018). The advantage of producing biofilm or forming a sessile stage of attached cells is protection from stressful environmental conditions and the ability to resist chemical agent ;as such, biofilms pose a major problem in treatment management(Mitchell et al., 2013).
Biofilm fnormation is a process that occurs in a defined order involving different phases. Adherence of yeast cells to a substrate is the initial important step toward biofilm formation. Adhesions mediated by electrostatic and hydrophobic forces and expression of agglutinin-like sequence genes(ALS).The *C. albicans* gene family of ALS is composed of eight genes encoding proteins localized mainly in the cell wall (Lohse et al., 2018)Expression of ALS mediates cell-to-cell attachment and attachment to different biotic and abiotic substrates .In *C. albicans*, a major group of adhesins is encoded by the ALS genes and these play acritical role in the earlier and late phases of biofilm formation, maintaining integrity and attachment of biofilm formation as illustrated in Figure1
.Thus, adhesion is an essential step toward colonization of epithelial cells by *Candida*. In this context, a high level of ALS gene expression was detected in *C. albicans* from women with VVC (Cheng et al., 2006).
During initiation of adhesion, proliferation of yeast cells takes place to forma basal cell line in a process which may extend from 2 to 4 hours in *C. albicans.* Filamentation will begin after 8 h of initial adhesion and is regulated by a different network of genes.*EFg1*is considered the core gene and the main regulatory factor, and acts by sequence-specific binding to DNA to regulate multiple genes involved in biofilm formation (Leng et al., 2001).During filamentation, deposition of extracellular matrix material occurs. Filamentation involving elongation of hyphaeis not a necessary step in biofilm formation as some yeast do not produce hyphae ;however, production of exopolymer molecules is the main concept defining biofilm communities. Exopolymer molecules are composed of proteins, chitins, DNA and1,3 β-glucancarbohydrates(Al-Fattani and Douglas, 2006).It is enclosed in biofilm to protect it from the outer stressful environment.

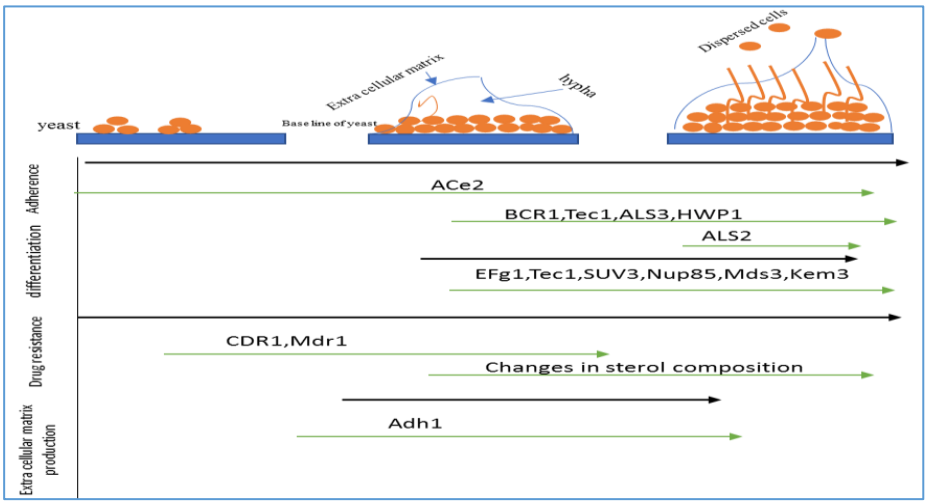

Figure 1:Overview of *C. albicans* biofilm development.
The thick black lines represent the phase(s) combined with categories of side phases. Within each phase a green arrow with listed protein or event in each phaseisdepicted. Image was adapted and modified from(Blankenship and Mitchell, 2006).

A range of environmental factors influence C.*albicans morphogenesis*, and induction of biofilm formation is stimulated under different conditions, including starvation, the presence of serum or N-acetylglucosamine, physiological temperature and CO_2, all of which promote the formation of hyphae. When *C. albicans*is grown in low pH it tends to grow in yeast form,while pH >7 promotes hypha production (Hall et al., 2011, Odds, 1988).The morphogenesis of switching from budding to hyphal stages of *C. albicans* has also been shown to be regulated by quorum sensing, the main quorum sensing in *C. albicans* involving farnesol, tyrosol and dodecanol.As a result of quorum sensing, high cell densities (> 10^7cells mL^{-1}) promote yeast growth, while low cell densities (< 10^7 cells mL^{-1}) favour hyphal formation (Hornby et al., 2001).

Biofilm formation is considered one of the main strategies used to escape from different innate immune cells and to invade epithelial cells.β-glucan (an example of a pathogen associated molecular pattern or PAMP) expression by cells at the top of the mature biofilm is masked facilitating escape from macrophages and other innate immune cells(Lohse et al., 2018).Moreover, upon phagocytosis of the planktonic stage, there is immediate up regulation of arginine synthesis to produce CO_2, a signal which mediates induction of hyphae formation within macrophages, thus enabling penetration of the cell membrane (Ghosh et al., 2009).*C. albicans* defective for the gene involved in hypha formation were not able to escape from macrophages(Lorenz et al., 2004). Therefore, outcomes of this interaction between macrophages and *C.albicans* hypha will shape the immune response. Importantly, gene expression by two forms–yeast and hypha– differ significantly.For example, high gene upregulation(an antigenic, zinc-binding cell surface protein) and Gpd2 (a glycerol-3-phosphate dehydrogenase that is found at the cell surface), during biofilm formation thatblocksthe host complement system (Gropp et al., 2009).

Biofilm and extracellular matrix provide protection from the environment, such as resistance to antifungal agents. However, their action as a physical barrier is not the only mode of persistence and resistance of biofilms or sessile cells against fungal agents. Differential gene regulation is involved and confers resistance of *Candida* biofilms such as by upregulation of *CDR1* and *CDR2* in the first phase of biofilm formation in the absence of drug(Fox et al., 2015).Moreover, a small subset of blastopore cells from a *C.albicans* biofilm have been described as highly resistant to amphotericin following adhesion due to changesincell membrane composition(LaFleur et al., 2006).Extracellular matrix varies in the proportion ofexo -polymer substances in different *Candida* species that impact on the eradication of biofilm by antifungal agents and on diffusion of drugs. Rates of diffusion for four classes of drugs –fluconazole, voriconazole, flucytosine and amphotericin B–have been investigated for *C. albicans, C. glabrata,C. krusei, C. parapsilosis* and *C. tropicalis*. Fluconazole permeated all species rapidly compared to flucytosineandall were generally lower in *C. albicans* strains. Moreover antifungal penetration was faster in *C. glabrata* or *C. krusei* than through biofilms of *C. parapsilosis* or *C. tropicalis*(Al-Fattani and Douglas, 2004).

Candida species are able to form biofilms on vaginal epitheliu ;however, their adhesion is influenced by the surrounding environment. Importantly, biofilm formation by *Candida*in the vagina is more likely to be a co-culture of multiple species of *Candida* and bacteria. Some studies have revealed that approximately20–34% of RVVC samples contain a pathogenic bacterium such as *Streptococcus agalactiae* or other *Candida* species.One main factor that is still controversial is the role of sex hormones inmediating biofilm formation(Alves et al., 2014).

1.7 Treatments and Immunotherapy

The protective mechanisms induced in the vagina during *Candida* infection in animal models have led to the proposal of vaccination or immunotherapy as anew strategy to treat vaginal *Candidiasis* . Luo identified the gene ***Hyr 1*** that functions as a hyphae co-expressing gene which is an important virulence factor for *C.albicans* , mediating resistance to phagocyte killing , as a promising approach to vaccination . Vaccination with a recombinant protein encoded by Hyr1p provided meaningful protection against disseminated candidiasis in a rat model , other anti-*Candida* vaccines ,from attenuated strains of *C.albicans* to a number of glycoconjugates of cell wall proteins , have demonstrated asignificant protective effect in experimental models . Another promising vaccine which has been evaluated in a rat model in intravaginal administration of recombinant proteinase secretory aspartyl proteinase . Immunized animals were protected against intravaginal *Candida* challenge as a result of increased local IgA and IgG.

Vaginal candidiasis and treatments

Vaginal candidiasis is one of the most common gynecological problems seen in primary care. *Candida albicans*account for 90% of the infection. It is reported that all women will suffer at least one episode of vaginal candidiasis during their lifetime and up to 40-55% of them having

recurrent vaginal candidiasis(Donders et al., 2010). Recurrent vaginal candidiasis is defined as at least four discrete episodes of symptomatic infection
occurring in a year(Donders et al., 2010). It is estimated that 5% of all women who have a single episode of vaginal candidiasis will experience chronic or recurrent infection. Recurrent vaginal candidiasis must be distinguished from persistent infection in which there is a symptom-free period in between the episodes of infection. Up to 33% of recurrent vaginal candidiasis is caused by non-albican species, which include C. *glabrata*, *C.tropicalis* and *Cparapsilosis*.Antifungal agents are central to clinical management of VVC. Unlike antimicrobial drugs, there are only four main classes of antifungal agents; the azoles (fluconazole, itraconazole, azaconazole, parconazole, and voriconazole), polyenes (conventional amphotericin B and its lipid formulations), echinocandins (anidulafungin, caspofungin), and the pyrimidine analogue flucytosine. The introduction and availability of these drugs are illustrated in Figure 2(Roemer and Krysan, 2014). Among all the antifungal agents used for *Candida* infections, only fluconazole and echinocandinsare recommended as first line agents for invasive candidiasis, and fluconazole for vaginitis infection.

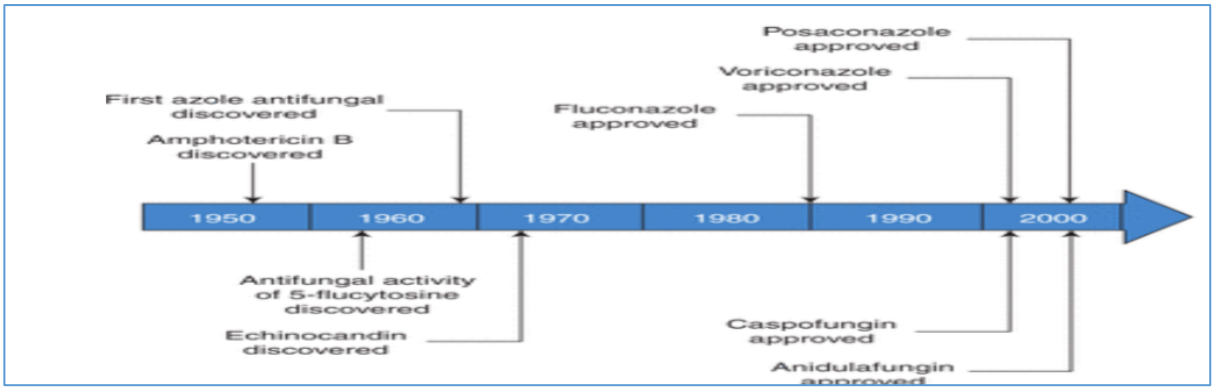

Figure 2.The development of antifungal drug classes and periods of use of antifungal drugs. Image is adapted from (Roemer and Krysan, 2014).

Antibiotic use

Use of antibiotics is considered a risk factor for developing VVC. The incidences of VVC and RVVC are affected by the duration and type of antimicrobial agents. Different epidemiological studies in different regions have demonstrated the increased incidence of VVC in women who have been using antibiotics in comparison with women who have not (Gonçalves et al., 2016). The association between VVC and antibiotic use is due to the depletion of the microflora, especially *Lactobacillus* communities, as *Lactobacillus* have different effective mechanisms to compete with and regulate the growth of *Candida.*

Amphotercin B (AMB)

AMB is polyene It is widely used in complicated in invasive candidiasis due to its broad spectrum of activity ,Unlike Triazole,AMB exerts its fungicidal activity by binding to ergosterol(Lewis, 2011). The main cell component of fungal cell wall forming channels through the ergosterol membrane leading to loss of intracellular compound and leaking of ions such as potassium and magnesium and cell destruction , this drug is relatively toxic due to its dose_ dependent side effect.AMB has broad spectrum of activity for majority of fungi and resistance is rarely reported in *Candida*
species,Some species are intrinsic or primary resistance to AMB such as *C.Lusitaniae* and other acquired resistance after long term treatment such as *C.albicans* such resistance has been detected in patient with mucosal infection over 5years period of treatment .Polyene _resistant *Candida*spp show a reduction of ergosterol in their cell membrane ,which lead to less binding of polyene structure of AMB to membrane ergosterol. This reduction in ergosterol might be result from mutation in their genes responsible for ergosterol biosynthesis.

Triazole

All azole agent share the same inhibiting mechanism of lanosterol 14- demethylase encoded by ERG11.This enzyme is essential enzyme in ergosterol synthesis pathway .Blocking this enzyme which stresses the cell membrane. Azole comprise two subclasses based on membrane of nitrogen atoms in the ring ,the first class include imidazoles and these contain two nitrogen atoms in the azole ring , the first subclass consist of six agents.miconazole, oxiconazole, econazole,ketoconazole ,tioconazole and clotrimazole(Muehlebach et al., 2018). A second class contains three nitrogen atoms in acyclic ring and include triazoles such as flucanazole , posaconazole , itraconazole ,terconazole and voriconazole. The triazole antifungal agent differ in their affinities for their drug target , which impact their activity spectrum .
Fluconazole have weakest interaction and thus exhibits the narrowest spectrum and its activity stretches to yeast but not moulds , however , posaconazole and voriconazole have a wider activity spectrum due to their strong binding to the drug target . Floconazole is fungistatic rather than fungicidal , inhibiting the growth of *Candida* and other fungal species.

ERG11 point mutation causes alternation and over expression of Erg11

Point mutation that change the affinity of the drug is one of the mechanisms that have been found in different *Candida* species, so far more than 140 _point mutation that have been sensitive and resistant strains , and 70_point mutations have been found in resistant *Candida* species (Table 2). The position of a point mutation will cause different effect on drug resistant , with some point mutations causing acquired resistance to flocanazole while others result in pan _drug resistance against multiple triazole .

Table 2: Summary of the molecular mechanisms conveying resistance to flucanazole ;

Mechanism	Gene(s)involved	Species
Drug target overexpression	*ERG11*	*C. albicans, C. parapsilosis, C. tropicalis*
Drug target alteration	*ERG11*	*C. albicans, C. parapsilosis, C. tropicalis, Candida auris*
Bypass pathways	*ERG3*	*C. albicans, C. tropicalis*
ABC transporters	*CDR1, CDR2, SNQ2, ABC1*	*C. albicans, Candida glabrata,*
MFS transporters	*MDR1, TPO3*	C. albicans, C.parapsilosis, C. tropicalis, *C. glabrata*
Aneuploidy/ loss of heterozygosity	*ERG11*	*C. albicans*

5-Flocytosine(5-FC):

The compound 5-fluorocytosine is one of the oldest antifungal agent known ,and was first synthesized in 1957 as anti-tumor agent ,and it proved to be insufficiently effective against tumers. Later was found to be active in experimental candidiasis and *Cryptococcosis* in mice . In 1988 it was approved as antifungal agent . 5-FC diffuses into *Candida* cells by the action of cytosine permease encoded by FCY2. Once inside the cells it is deaminated and converted to 5-fluorouracil (5-fu) by cytosine deaminase (Ellepola and Samaranayake, 1998). Then 5-FU is converted to 5-fluorouridine monophosphate by uracil phosphoribosyl transferase (UPRTase) ,encoded by FCY1 and FUR1 genes . The latter compound is incorporated into RNA in place of UTP and blocks RNA biosynthesis. Flucytosine cannot be used as monotherapy as resistance quickly due to point mutation in the genes FCY2, FCY1 and FUR1. In vitro and in animal models, amphotericin B and 5FC show synergistic activity against a number of *Candida* spp. Studies in vitro found that the combination has a higher rate of killing so is used to treat females with RVVC (Table 3) .

Primary Resistance species are defined as species exhibiting inherent resistance to one or more agent of antifungal drug classes .

Acquired Resistancewhich is a characteristic of almost all representative strains of specific *Candida* species and is predictive of clinical failure .

Table 3: Intrinsic susceptibility patterns for *Candida* species**,** for two systemic antifungal agents .

Species	Fluconazole	Amphotericin B
C.albicans	S	S
C. dubliniensis	S	S
C. glabrata	I	S
C. krusei	R	S
C. parapsilosis	S	S
C. tropicalis	S	S

2. The Aim of the Study

This review outlines selected aspects in the current understanding of BV and *C. albicans* pathogenesis and interactions with the host, and refer to the relationship between presence of pathogenic microorganisms in reproductive tract and infertility is widely document.Candidiasis is adapt to adhere to host tissues pass though epithelial *Candida* can cause disease this study present several antibiotics, tools developed in the postgenomic era to study these topics.

3. Conclusions and Recommendations

The interactions between BV, *C.albicans* and the host are critical for persistence pathogenesis of the pathogen and the immune defense of the host. *Candida* adhesion to spermatozoa and agglutination inhibiting human sperm motility and decreasing sperm viability have been described. In another case report *C. albicans* was detected in the medium where spermatozoa were co-incubated with oocytes but had failed to fertilize . Thus, *Candida* could be implicated in infertility, but more detailed characterisation of *Candida* found in the male genitourinary tract and oral cavity is needed.

Multiple ways are used to penetrate the host tissues. For instance, hydrolytic enzymes secretion, cell surface adhesion, and hyfae formation. Phenotypic switching also helps *C.albicans* adapt to changing environments within host. All these factors increase the host immune responses. **5-Flocytosine (5-FC)**Triazole Amphotercin B considerable antifungal properties against *Candida* sp.. They possess considerable anti-adhesion and, anti biofilm effects , and inhibitory activity. This review presents an outline of several important topics. Furthermore, the development of genome wide technologies for analysing pathogene host interactions has dramatically increased and will provide important insights for other fungal pathogens.

3.2 Recommendations

An increase risk with a diagnosis of Candidosis and BV infections which increased medical problems. There is an unmet need to more accurately define technique to detect BV and candidosis in both pregnant and non-pregnant women. Also, we need to find advanced factors that increase the susceptibility of vaginal pathogens.

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الخلاصة

ان الاصابات المهبل البكتيريا (BV) والفطرية توثر على صحة المرآة وكذلك الاطفال حديثي الولادة . حيث وجد ان هناك العديد من البكتريا المرضية مثل *Streptococcus*sp, *Lactobacillus reuteri* *Lactobacillus rhamnosus*تصيب النساء . بالاضافة الى الاصابة البكتيرية وجد ان هناك ٧٥% من النساء يصابن بداء المبيضات المهبلي والذي وجد انه له علاقه بالعقم. ارتبطت اصابه المهبل البكتيريه بالولاده المبكرة وامراض التهاب الحوض لدى النساء. تظهر الدراسات المختبرية أيضًا أن داء المبيضات المهبلي يؤثر على جودة الحيوانات المنوية ممايؤدي الى العقم عند الذكور. ومع ذلك ، فقد بحثت دراسات قليلة تأثير تنوع الاصابات البكتيرية والكانديدا على العقم.

كما وجدت الدراسات الحديثة انه معظم النساء اللواتي لديهن اصابات بكتيرية وداء المبيضات المهبلي المتكرر (VVC / RVVC) لديهم مستعمرات مايكروبية في كل من الاجزاء المهبلية والفموية مع نفس نوع السلالة المايكروبية ، وقد لوحظ تنوع بين السلالات بين الحين والآخر للأفراد. تم الكشف عن تنوع جيني واضح في الأزواج الذين يخضعون لعلاج مضاد للفطريات. كما لوحظت اختلافات في الاستجابة المناعية على أساس جنس المشارك بدلاً من حالة الخصوبة. كما إن اختلاف الاحياء المايكروبيه قد يشيرالى وجود أنواع الكانددا او البكتريا التي تغطي الظهارة المهبلية في بعض الأشخاص المصابين بالتهاب المهبل البكتيري إلى أن الأغشية الحيوية قد تساهم في هذه الحالة بزيادة الامراضية والتفاعل مع جسم المضيف. ان الغرض من هذه الدراسة هومراجعة الجوانب المختارة في الفهم الحالي للاصابات البكتيرية و *C. albicans* وتفاعلها مع المضيف ، وفهم دور العديد من المضادات الحيوية والتقنيات الجينية التي تم تطويرها لدراسة هذه الموضوع .

وزارة التعليم العالي والبحث العلمي
جامعة ديالى/كلية العلوم
قسم التقانة الاحيائية
الدراسة الصباحية

دراسة التاثير المؤازر للاصابة بالكانددا والبكتريا المهبلية على العقم

بحث تخرج مقدم الى
مجلس قسم التقانة الاحيائية/كلية العلوم/جامعة ديالى
وهو جزء من متطلبات نيل درجة البكالوريوس في التقانة الاحيائية

من قبل

اسراء قتيبة احمد و الاء علي عبدالله و جيلان مقداد كريم
و فتون فاضل احمد و فاطمة عبدالمنعم هندي

باشراف

ا.م.د. علياء معن عبد الحميد

٢٠٢٠م – ١٤٤١هـ