Prevalence and Risk factors of Vulvovaginal Candidiasis during pregnancy: A Review

By-

Tasfia Latif Disha

Student ID: 16136004

A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of
Bachelor of Science in Biotechnology

Department of Mathematics and Natural Sciences
BRAC UNIVERSITY
April 2021

Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing the degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all the main sources of help.

Student's Full Name & Signature:

Tasfia Latif Disha
Student ID: 16136004

Approval

The thesis/project titled **"Prevalence and Risk factors of Vulvovaginal Candidiasis during pregnancy: A Review"** submitted by

1. Tasfia Latif Disha (16136004)

of Spring, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Science in Biotechnology on "date to be given" of April 2021.

Examining Committee:

Supervisor:
(Member)

_____
Fahim Kabir Monjurul Haque, PhD
Assistant Professor, Department of Mathematics and Natural Sciences
Brac University

Program Coordinator:
(Member)

_____
Iftekhar Bin Naser, PhD
Assistant Professor, Department of Mathematics and Natural Sciences
Brac University

Departmental Head:
(Chairman)

_____
A F M Yusuf Haider, PhD
Professor and Chairperson, Department of Mathematics and Natural Sciences
Brac University

Acknowledgment

First of all, praises and thanks to Almighty Allah for the continuous blessings for which I could complete my thesis. I would also like to thank my family for the support and encouragement without which I could not have completed my thesis.

I would like to offer my sincere gratitude to my supervisor, Dr. Fahim Kabir Monjurul Haque, Assistant Professor, Department of Mathematics and Natural Sciences, Brac University for his insights and guidance which inspired me during my thesis. It was a great opportunity to work under him which will be proven beneficial in the future.

Lastly, I would like to thank my friends and well-wishers, Dolan Karmaker, Monika Barua, Sabrina Binte Azad, Khalid Hossain Olive, Sheikh Abdul Alim, Rafid Hasan Arnob, Shimul Saha, Nosin Sharmili for their positive words which helped me to concentrate better. I would also like to convey my heartfelt gratitude to Nusrat Jalal who has been a constant support to me.

I deeply appreciate all these aforementioned people for their presence which helped me either academically or mentally, to successfully complete what I had started. To me, this was an opportunity to learn many things that covers my area of interest. Hence, I believe that the knowledge I have gathered during my thesis will be proven helpful in my near future.

Tasfia Latif Disha

Student ID: 16136004

Abstract

Vulvovaginal candidiasis (VVC) is an infection of the vagina caused by yeast, especially *Candida* spp. Although VVC is common among reproductive-age women, prevalence studies notice its uprise to 30% during pregnancy, especially in the last trimester. Recent studies have considered it a severe problem due to the emerging evidence showing the association of VVC with a higher risk of pregnancy-related complications (e.g., premature rupture of membranes, preterm labor, chorioamnionitis, and congenital cutaneous candidiasis). In this review, we have reassessed and summarized the prevalence of VVC in pregnant women and analyzed the association of several factors to the increased risk of VVC during pregnancy in different regions of the world. Data collected from various studies showed the highest prevalence of VVC during pregnancy, mostly in Asian and African countries (90.38%, 62.2%, 61.5% in Kenya, Nigeria, and Yemen, respectively). The prevalence rate of VVC during pregnancy was also found out to differ with age, gestation period, parity, educational status, and socioeconomic level. In the majority of the cases, women in their 3rd trimester showed the highest prevalence of VVC, and the rate of Candida colonization was also higher in pregnant women with no primary education. Multi-gravidae mothers and women with multipara of parity were found to show the highest prevalence of VVC in most cases. *Candida albicans* was identified as the responsible organism for VVC in most studies, yet a remarkable increase in the incidence rate of non-*albicans Candida* spp. particularly *Candida glabrata, Candida krusei, Candida tropicalis* as the causative agent of VVC during pregnancy had been noticed in other studies. Some pregnancy-related factors (e.g., weakened immunity; elevated level of sex hormones, glycogen deposition; low vaginal pH; decreased cell-mediated immunity) and several clinical and behavioral factors were suggested as potential risk factors of candidiasis during pregnancy. In our analysis, we couldn't find any difference in

prevalence between symptomatic and asymptomatic VVC cases. While some literature found a higher expression of symptomatic VVC among pregnant women, others found out asymptomatic VVC at greater rates. Furthermore, in our analysis, no definitive association could be established between the prevalence of VVC and factors such as Diabetes mellitus, HIV infection, previous candidiasis, use of antibiotics, oral contraceptives, and intrauterine device despite of the fact that some authors found an association between them.

Keywords

Vulvovaginal candidiasis, VVC, Candida vaginitis, Pregnancy, Prevalence, Risk factors.

Table of Contents

List of Tables

List of Figures

List of Acronyms

Acronyms	Explanation
VVC	Vulvovaginal candidiasis
NAC	Non – *albicans Candida*
DM	Diabetes mellitus
pH	Potential of hydrogen
HIV	Human immunodeficiency virus
IUD	Intrauterine device

Chapter 1

Introduction

Vaginal Candida infections are commonly called ‘‘Candida vaginitis’’ or ‘‘vulvovaginal candidiasis’’ (VVC) (Achkar & Fries, 2010). Vulvovaginal candidiasis is an infection of the estrogenized vagina and the vestibulum, which can extend to the outside of the labia minora, the labia majora and the intercrural region (Mendling & Brasch, 2012). It is considered as the 2Nd most common among many causes of vaginitis after bacterial vaginosis (Achkar & Fries, 2010). It is produced most often by the overabundance of an opportunistic pathogenic yeast, *Candida albicans* (approximately 90%) which is a common member of the vaginal flora (van Schalkwyk et al., 2015; Gow & Yadav, 2017; Sobel, 2007). This dimorphic yeast, a commensal that colonizes skin, the gastrointestinal and the reproductive tracts and can be found in the vaginal tracts of 20 to 30% of healthy asymptomatic women at any single point in time. If the balance between colonizing yeast and the host gets temporarily disturbed then Candida can cause infection like VVC, that is associated with clinical signs of inflammation (Achkar & Fries, 2010). However, other *Candida* species such as *glabrata, parapsilosis* and *tropicalis* are also emerging as identifiable causes of VVC (van Schalkwyk et al., 2015).

On the basis of episodic frequency, vulvovaginal candidiasis is usually classified as either sporadic or recurrent (J. D. Sobel et al., 1998). Uncomplicated or sporadic VVC includes mild to moderate clinical signs and symptoms such as a thick cottage-cheese–like discharge, vaginal and vulvar pruritus, pain, burning, erythema, and/or edema along with external dysuria and dyspareunia (van Schalkwyk et al., 2015). Complicated or recurrent VVC may be defined as that which has recurrent

episodes (4 or more episodes in a 12month period), associated with severe symptoms (Achkar & Fries, 2010).

Around 75% of all women experience at least one episode of VVC during their childbearing years, and among them about half have at least one recurrence (J. D. Sobel et al., 1998). Vaginal colonization of *Candida* species occurs in at least 20 % of all women but this statistic rises to 30% in pregnancy (Mendling & Brasch, 2012). During pregnancy, Vulvovaginal candidiasis is considered more common and difficult to eradicate because several normal and expected physiological changes in the genitourinary-tract favor the growth of Candida (Kamath et al., 2013 ; J. D. Sobel et al., 1998).

Some evidences in recent days show the association of candidiasis with an increased risk of complications during pregnancy, such as premature rupture of membranes and poor pregnancy outcome such as, preterm labor, chorioamnionitis, and congenital cutaneous candidiasis during pregnancy (Mølgaard-Nielsen et al., 2016 ; Meizoso et al., 2008). According to the literature, the incidence of vaginal colonization with Candida species in pregnant women is considered to be approximately 10–50% (Guzel et al., 2011) and this is a major problem as pregnant women can even contaminate their infants from 25% up to 65% which will result in invasive neonatal candidiasis (Bliss et al., 2008; Al-Rusan et al., 2017). Evidences showed that women with untreated asymptomatic candidiasis had a higher spontaneous preterm birth rate compared to those who do not have candidiasis (6.25 versus 2.99 %) (Aguin & Sobel, 2015).

Multiple risk factors, for instance, pregnancy, immunosuppression, HIV infection, using contraceptive, antibiotic use and diabetes are recognized to increase the susceptibility to VVC (Aguin & Sobel, 2015 ; Tsega & Mekonnen, 2019). Pregnancy-related factors such as decreased cell-mediated immunity, increased estrogen levels and increased vaginal mucosal glycogen

production is likely to cause the increased risk of VVC and asymptomatic colonization in pregnancy (Aguin & Sobel, 2015).

To date, a collective information on the prevalence of VVC during pregnancy and on the factors associated with VVC in pregnant women across the world is not available that much. So, in this review we have aimed to compile the recent data regarding the prevalence and risk factors of VVC during pregnancy. This review study has the following purposes: (1) to review previous papers on the prevalence of VVC; (2) to reassess and summarize the associated factors with VVC during pregnancy and (3) to give an overview on the differences in prevalence and factors of VVC found out among pregnant women in different regions of the world.

Chapter 2

Research Methodology

2.1 Search strategy

Databases such as Google Scholar, PubMed and ScienceDirect were used to find out scientific literature relevant to the topic. While searching, keywords such as vulvovaginal candidiasis, candida vaginitis, prevalence, pregnancy, risk factors, VVC had been used. The search result was kept specific by using Boolean operators “AND” “OR” and “NOT”. Original research and review articles with good number of citations were chosen to retrieve relatable information with the subject.

2.2 Inclusion criteria

Original literature that described the prevalence of VVC in pregnant women, the risk factors associated with VVC during pregnancy, the *Candida* and non-*albicans Candida* spp. distribution among pregnant women were included. Moreover, literature that mentioned the symptoms and complications of VVC during pregnancy were also included in a brief manner.

2.3 Exclusion criteria

Literature that only stated the prevalence of bacterial vaginosis and /or trichomoniasis, the antibiotic resistance of *Candida* spp., the diagnosis and treatment of VVC were excluded. Along with that, papers that just stated the prevalence of VVC among non-pregnant or reproductive age women were also excluded.

Chapter 3

Prevalence of Vulvovaginal Candidiasis during pregnancy

3.1 Higher prevalence of VVC during pregnancy

Multiple studies have carried out a comparative study between pregnant and non-pregnant women and found out that the prevalence of VVC is higher in pregnant women than that in nonpregnant women (shown in Figure 1). Such a study was by Babić & Hukić (2010) where significantly increased number of positive microscopic findings were in pregnant women 40.9% (83/203) compared to 23.8% (58/244) in non-pregnant women.

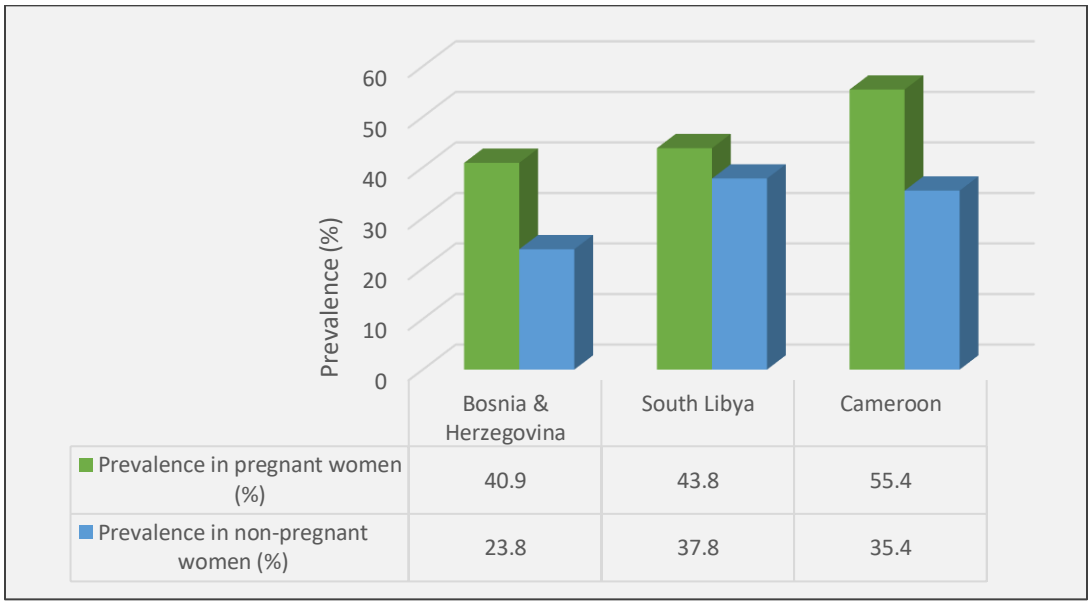

Figure 1. Difference in prevalence of VVC between pregnant & non-pregnant women.

Figure 1 shows the similar type of results in South Libya with 43.8% (Altayyar et al., 2016) and in Cameroon (Toua et al., 2013) with 55.4% prevalence. Grigoriou et al.(2006) performed a same type of study consistent with this result where the prevalence of VVC among 3,791 non-pregnant

and 952 pregnant women with signs and symptoms of vaginitis were tested and *Candida* spp. were recovered from 299 (7.9%) of the non-pregnant women and 277 (29.1%) of the pregnant women. Thus, these results highlight the higher prevalence of VVC during pregnancy.

3.2 Region wise total prevalence of VVC among pregnant women

In our analysis, we have found that the prevalence of VVC in pregnant women differs from region to region. In USA, the prevalence of moderate to heavy levels of vaginal candidiasis among pregnant women is estimated to be 10% (Cotch et al., 1998). The prevalence of vulvovaginal candidiasis during pregnancy has been observed to be 17-90% in our analysis (Table 1). The prevalence of VVC among pregnant women in different regions across the world has been presented in Table 1.

Place	No. of studied patients	Prevalence (%)	Citation
Adana, Turkey	372	37.4	(Guzel et al., 2011)
Anambra State, Nigeria	300	30	(Okonkwo & Umeanaeto, 2011)
Ardabil, Iran	408	35	(Mohammadi-Ghalehbin et al., 2017)
Argentina	210	24.8	(Mucci et al., 2017)
Burkina Faso	229	22.71	(Sangaré et al., 2018)
Enugu State, Nigeria	901	62.2	(Akah et al., 2010)
Ghana	176	30.7	(Waikhom et al., 2020)
Ibb, Yemen	218	61.5	(Edrees et al., 2020)
Janakpur, Nepal	157	35	(Yadav & Prakash, 2016)
Kathmandu, Nepal	200	29.5	(Shrestha et al., 2011)
Kenya	104	90.38	(Nelson et al., 2013)
Lebanon	221	44.8	(Ghaddar et al., 2019)
Lebanon	258	39	(Ghaddar et al., 2020)
Maroua, Cameroon	112	55.4	(Toua et al., 2013)

Mato Grosso, Brazil	404	44.8	(Dias et al., 2011)
Middle Belt of Ghana	589	36.5	(Konadu et al., 2019)
Natal, Brazil	41	48.78	(Brandão et al., 2018)
Northwest Ethiopia	384	25	(Tsega & Mekonnen, 2019)
North-west Nigeria	288	60.8	(Nnadi & Singh, 2017)
Sana'a, Yemen	190	51.6	(Al-Rukeimi et al., 2020)
Sarajevo, Bosnia & Herzegovina	203	40.9	(Babić & Hukić, 2010)
Selangor, Malaysia	1163	17.2	(Masri et al., 2015)
South Karnataka, India	118	42.37	(Kanagal, 2014)
South Libya	150	43.8	(Altayyar et al., 2016)
Southwestern Nigeria	100	36	(Olowe et al., 2014)
Taif, Saudi Arabia	1207	70.2	(Al-Aali, 2013)
Tunisia	2160	32.87	(Mtibaa et al., 2017)

Table 1: The prevalence of VVC during pregnancy in different regions of the world. Data has been organized alphabetically.

According to the data in Table 1, the highest prevalence of VVC to be noticed is 90.38% in Kenya, a study conducted by Nelson et al., 2013. Also, significant prevalence of VVC with 62.2%, 60.8% & 61.5% has been observed in Enugu state, Nigeria (Akah et al., 2010) ; North-west Nigeria (Nnadi & Singh, 2017) & Ibb, Yemen (Edrees et al., 2020) respectively. On the contrary, a study performed by Masri et al., 2015 in Malaysia has shown the lowest prevalence of VVC, that is 17.2% during pregnancy. Rest of the data has showed moderate to high levels of prevalence of VVC among pregnant women around the world (Table 1).The widespread prevalence of VVC among child-bearing women can be perceived through this data. The differences in the prevalence rates across the world can be because of factors like geographic, ethnic and socioeconomic along with varying sampling and culturing techniques (Yadav & Prakash, 2016).

3.3 Prevalence of VVC according to presence of symptoms

Vulvovaginal candidiasis incorporates the range of patients both with and without symptoms having positive cultures of *Candida* spp. and those might phenotypically extend from having an appearance of florid, severe disease to absolutely no appearance of signs and symptoms (J. D. Sobel et al., 1998). Based on the absence or presence of symptoms, the prevalence of VVC among pregnant women has been shown in Table 2.

Place	Asymptomatic (%)	Symptomatic (%)	Citation
Adana, Turkey	37.5	61.2	(Guzel et al., 2011)
Argentina	61.9	38.1	(Mucci et al., 2017)
Burkina Faso	70.74	29. 26	(Sangaré et al., 2018)
Enugu State, Nigeria	27	70	(Akah et al., 2010)
Ghana	18.5	81.5	(Waikhom et al., 2020)
Janakpur, Nepal	40.12	59.87	(Yadav & Prakash, 2016)
Kathmandu, Nepal	67.9	32.1	(Shrestha et al., 2011)
Middle Belt of Ghana	68.2	31.8	(Konadu et al., 2019)
Northwest, Ethiopia	18.7	40.5	(Tsega & Mekonnen, 2019)
Sana'a, Yemen	22.3	86.2	(Al-Rukeimi et al., 2020)
South Karnataka, India	18	82	(Kanagal, 2014)

Table 2: The prevalence of VVC according to the presence of symptoms. Data has been arranged alphabetically.

During pregnancy, a higher prevalence of symptomatic infection caused by *Candida* species was found out by several studies. Table 2 shows that majority of the places had detected higher

prevalence of symptomatic VVC. Among them, the highest symptomatic prevalence was recorded in Sana'a, Yemen (Al-Rukeimi et al., 2020) that is 86.2%. Edrees et al.(2020) and Ghaddar et al.(2019) had also found higher prevalence of *Candida* (+) spp. among pregnant women in Ibb, Yemen and Lebanon with 61.2% and 82% respectively. Along with that, similar results were found out in Mato Grosso, Brazil (Dias et al., 2011),Tunisia (Mtibaa et al., 2017) and North-west Nigeria (Nnadi & Singh, 2017) where majority had expressed sign and symptoms of VVC.

Yet, there are other studies that showed that pregnant women were more likely to experience an asymptomatic Candida infection. Mucci et al.(2017) had found 61.9% asymptomatic VVC among pregnant women in Argentina (Table 2). 67.9%, 68.2% and 70.74% asymptomatic *Candida* (+) spp. were detected in Kathmandu, Nepal (Shrestha et al., 2011), Middle Belt of Ghana (Konadu et al., 2019) and Burkina Faso (Sangaré et al., 2018) respectively. These results were in consistent with the previous one. These results justify the higher occurrence of asymptomatic VVC during pregnancy. On the other hand, Okonkwo & Umeanaeto (2011) found no significant difference in the prevalence between symptomatic and asymptomatic pregnant women.

3.4 Prevalence of different species of *Candida* among pregnant women

In a study, *Candida albicans* has been isolated from more than 80% of specimens obtained from women with vulvovaginal candidiasis and has been considered as the most common causative yeast for VVC (Kinghorn, 1991). A 5 yearlong epidemiological survey on the causative agents of VVC had also found *Candida albicans* as the most prevalent cause in 87.9% of cases (Paulitsch et al., 2006). The species that have been mostly identified in several studies are *C. albicans, C. glabrata, C. krusei, C. tropicalis, C. lypolytica, C. kefyr, C. famta, C. parapsilosis* and *C. dubliniensis*. In Table 3, prevalence of *C. albicans* and non-*albicans Candida* spp. isolated from pregnant women around many parts of the world has been presented. It also shows the dominance

of *C. albicans* over other non-*albicans Candida* spp. in majority of the cases. Highest prevalence of *C. albicans* that had been recorded from the samples of pregnant women was 95% in Natal, Brazil (Brandão et al., 2018). Dias et al., (2011) also had found a prevalence of 92.3% for *C. albicans* in Mato Grosso, Brazil. In some other areas like Sarajevo, Bosnia & Herzegovina (Babić & Hukić, 2010), Malaysia (Masri et al., 2015) and Argentina (Mucci et al., 2017) had detected significant prevalence of *C. albicans* which was 87.4%, 83.5% and 80.7 % respectively.

C. glabrata has been considered as the most common associated species with VVC among NAC spp. (Ghaddar et al., 2019) which is in consistent with the data mentioned in Table 3. On the other hand, Edrees et al.(2020) showed the higher prevalence of *C. tropicalis* (21.64%) over *C. glabrata* (11.19%) . Tsega & Mekonnen (2019) also showed similar type of result where *C. krusei* (21.9%) was higher than *C. glabrata* (17.7%). Ahmad & Khan (2009) had found *C. parapsilosis* to be the second most prevalent non-*albicans Candida* species after *C. glabrata*. But, in Table 3, the most commonly detected non-*albicans candida* spp. after *C. glabrata* were *C. krusei and C. tropicalis.*

Place		NAC (%)							
	C. albicans (%)	*C. glabrata* (%)	*C. krusei* (%)	*C. tropicalis* (%)	*C. lypolytica* (%)	*C. kefyr* (%)	*C. famata* (%)	*C. parapsilosis* (%)	*C. dubliniensis* (%)
Adana, Turkey (Guzel et al., 2011)	58.0	19	2.9	13.2		2.4	1.5	0.5	0.5
Argentina (Mucci et al., 2017)	80.7	3.8							3.8
Burkina Faso (Sangaré et al., 2018)	40.39	32.69	11.54	15.38					
Ghana (Waikhom et al., 2020)	25.9	57.4	11.1					5.4	

Ibb, Yemen (Edrees et al., 2020)	61.2	11.19		21.64		5.97			
Janakpur, Nepal (Yadav & Prakash, 2016)	64.04	12.35	3.37	5.61					10.11
Kenya (Nelson et al., 2013)	63.83	29.79	2.13	3.19				1.06	
Lebanon (Ghaddar et al., 2019)	43.4	44.5	12.1						
Lebanon (Ghaddar et al., 2020)	42	41	17						
Malaysia (Masri et al., 2015)	83.5	16					0.05		
Mato Grosso, Brazil (Dias et al., 2011)	92.3	2.2	3.3	1.1				1.1	
Natal, Brazil (Brandão et al., 2018)	95	5							
Northwest, Ethiopia (Tsega & Mekonnen, 2019)	56.25	17.7	21.96	1					
Sana'a, Yemen (Al-Rukeimi et al., 2020)	39.5	4.7			3.2		2.1		0.52
Sarajevo, Bosnia & Herzegovina (Babić & Hukić, 2010)	87.4	4.2	3.2	2.1					
South Karnataka, India (Kanagal, 2014)	69.23	23.07		7.69					
Taif, Saudi Arabia (Al-Aali, 2013)	70.2	16.5		3.3	2.6	0.6			

Tunisia (Mtibaa et al., 2017)	76.61	17.18	1.54	1.4		0.56

Table 3: The distribution of different species of *Candida* isolated from pregnant women across the world. Data has been arranged alphabetically.

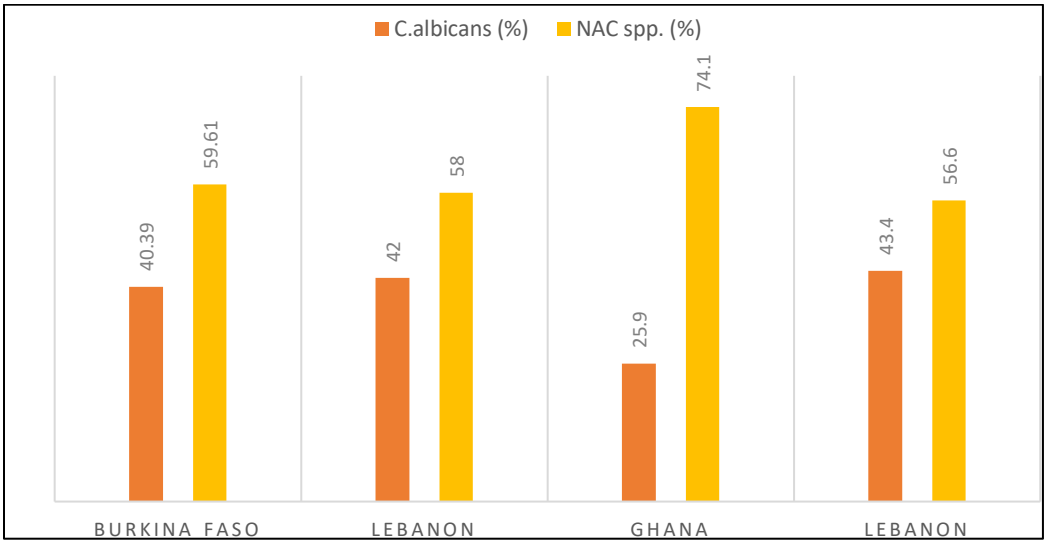

Figure 2: Difference in the distribution of *C. albicans* & non-*albicans Candida* spp.

Although, *Candida albicans* has been found to be responsible for the maximum number of symptoms associated with the vaginal candidiasis in numerous studies worldwide but a noticeable increase in the percentage of isolation rate of non-*albicans Candida* spp. together with infections caused by them has been observed in several Asian and African countries in the past three decades (Ghaddar et al., 2019 ; Babić & Hukić, 2010). Multiple studies have found the higher prevalence of non-*albicans Candida* spp. over *Candida albicans* (showed in Figure 2). Waikhom et al.(2020) found the highest cumulative prevalence of NAC spp., 74.1% where *C. glabrata* alone accounted for 57.4% of prevalence among pregnant women in Ho municipality, Ghana. Ghaddar et al.(2020) and Sangaré et al. (2018) also found 58% and 59.61% prevalence of NAC spp. respectively.

Another study where 56.6% (*C. glabrata* 44.5%) prevalence of NAC spp. was observed in Lebanon (Ghaddar et al., 2019), this result correlated with the previous mentioned ones (Figure 2). It has been seen in multiple studies evaluating the prevalence of vulvovaginal candidiasis among pregnant women that the distribution of isolated *Candida* species is different from country to country and it remarkably depends on several risk factors such as age, hygienic habits and disease history (Ghaddar et al., 2019).

3.5 Age group wise distribution of VVC

Several studies had divided their study population in different age groups to identify the age group with highest prevalence of VVC among studied pregnant women in those respective studies. Based on those data, Table 4 has been formed.

Place	Age groups (years)	Prevalence (%)	Citation
Ho municipality, Ghana	< 20	11.1	(Waikhom et al., 2020)
	20 - 29	**44.4**	
	30 - 39	40.7	
	40 - 49	3.7	
Ibb, Yemen	18 – 27	8.95	(Edrees et al., 2020)
	28 – 37	**54.48**	
	38 – 47	36.57	
Janakpur, Nepal	15 – 20	19.10	(Yadav & Prakash, 2016)
	21 – 25	**40.44**	
	26 – 30	32.58	
	> 30	7.86	
Karnataka, India	20 – 25	18	(Kanagal, 2014)
	26 – 30	**64**	
	30 – 35	12	
	> 35	06	
Kenya	15 – 25	26	(Nelson et al., 2013)
	26 – 35	**60**	
	36 – 45	12	
	> 46	2	

Lebanon	20 – 25	12.5	(Ghaddar et al., 2019)
	26 – 30	**34.1**	
	31 – 40	31	
Maroua, Cameroon	< 18	4.8	(Toua et al., 2013)
	18 – 24	25.8	
	25 – 31	**46.8**	
	32 – 38	16.1	
	≥ 39	6.5	
North-west Ethiopia	**18 – 25**	**50.5**	(Tsega & Mekonnen, 2019)
	26 – 33	42.7	
	34 – 40	6.8	
Northwest Nigeria	16 – 20	8	(Nnadi & Singh, 2017)
	21 – 25	33.7	
	26 – 30	**37.1**	
	31 – 35	16	
	36 – 40	5.1	
Sana'a, Yemen	< 20	33.3	(Al-Rukeimi et al., 2020)
	20 – 24	**61**	
	25 – 29	41.3	
	30 – 34	42.8	
South Libya	**16 – 25**	**46.7**	(Altayyar et al., 2016)
	26 – 35	40.7	
	36 – 45	36.1	
Southwestern Nigeria	21 – 25	14.3	(Olowe et al., 2014)
	26 – 30	33.9	
	31 – 35	**46.9**	
	36 – 40	20	
Taif, Saudi Arabia	15 – 19	5.1	(Al-Aali, 2013)
	20 – 24	6.6	
	25 – 29	**68.3**	
	30 – 34	9.6	
	35 – 39	7.8	
	40 – 44	3.4	

Table 4: Prevalence of VVC among pregnant women according to their age. Data has been arranged alphabetically. The age groups with highest prevalence in respective studies have been highlighted.

The range of age groups with highest occurrence of VVC in different studies is between 16 to 37 years. Among the age groups in Table 4, the highest prevalence of VVC has been noticed in the

age group 25 – 29 years with 68.3% (Al-Aali, 2013). The other age groups of pregnant women with almost close prevalence are 26 – 30 years (Kanagal, 2014), 20 -24 years (Al-Rukeimi et al., 2020) and 26 – 35 years (Nelson et al., 2013). So, there is not any common single age group constantly with significant prevalence among different studies rather it varies from region to region. The possible reasons might be the relation of these results to the high sexual activity of participants belonging to the respective groups and also to the fact that these women use drugs and contraceptives indiscriminately to prevent pregnancy (Altayyar et al., 2016). Another reason could be that the association of age group with prevalence of VVC was affected by other variables (Al-Rukeimi et al., 2020).

3.6 Gestational period wise distribution of VVC

Multiple studies had identified the gestation period in which the prevalence of VVC was the highest in the respective study to find out any correlation between the gestion period and the prevalence of VVC during pregnancy. Table 5 shows the data collected from those studies.

Place	No. of trimester	Prevalence (%)	Citation
Burkina Faso	1st	22.78	(Sangaré et al., 2018)
	2nd	17.78	
	3rd	**24.71**	
Ho municipality, Ghana	1st	16.7	(Waikhom et al., 2020)
	2nd	25.9	
	3rd	**57.4**	
Janakpur, Nepal	1st	34.11	(Yadav & Prakash, 2016)
	2nd	**55**	
	3rd	10.89	
Karnataka, India	1st	16	(Kanagal, 2014)
	2nd	**54**	
	3rd	30	
Kenya	1st	10.63	(Nelson et al., 2013)
	2nd	21.28	
	3rd	**68.09**	

Northwest, Nigeria	1st 2nd **3rd**	0.69 6.94 **52.7**	(Nnadi & Singh, 2017)
Sana'a, Yemen	**1st** 2nd 3rd	**61.1** 46.2 50	(Al-Rukeimi et al., 2020)
Southwestern Nigeria	1st 2nd **3rd**	2.1 37.5 **92.1**	(Olowe et al., 2014)

Table 5: Prevalence of VVC during pregnancy according to the no. of trimester. Data has been organized alphabetically and gestational period with highest prevalence has been highlighted.

According to Kinghorn (1991), prevalence of VVC increases with the progression of pregnancy, specially, in the last trimester. Majority of the prevalence mentioned in Table 5 are in consistent with this where most of the highest prevalence had been observed in the 3rd trimester. Among all of them, a study by Olowe et al. (2014) had found the highest (93%) prevalence of VVC in the last trimester of pregnancy wheras first and second trimester also had shown highest occurrence of VVC in a couple of studies (Table 5). In case of gestation period, this difference in rates of VVC could be due to the difference in sample size and study participants (Tsega & Mekonnen, 2019). Therefore, it can not be said strongly that prevalence increases only with the gestational period as women in their 1st and 2nd trimester also had shown higher risk of getting vulvovaginal candidiasis (Masri et al., 2015). On the other side, Tsega & Mekonnen (2019) did not find any significant differences between gestational period and *Candida* colonization.

3.7 Socioeconomic level, educational status & parity wise distribution of VVC

Al-Rukeimi et al. (2020) and Edrees et al. (2020) had found the highest prevalence of VVC among pregnant women from low socio economic level (60.4%) and from rural area (65%) respectively.

Toua et al. (2013) had found out highest prevalence in the unemployed (66.1 %) group of pregnant women. Similarly, unemployed women showed highest prevalence that is 44.94% in a study by Yadav & Prakash (2016) whereas another two studies by Al-Aali (2013) and Shrestha et al. (2011) had showed highest prevalence in women from teacher (76.6%) and agricultural (48.4%) occupation respectively. These data are shown in Figure 3.

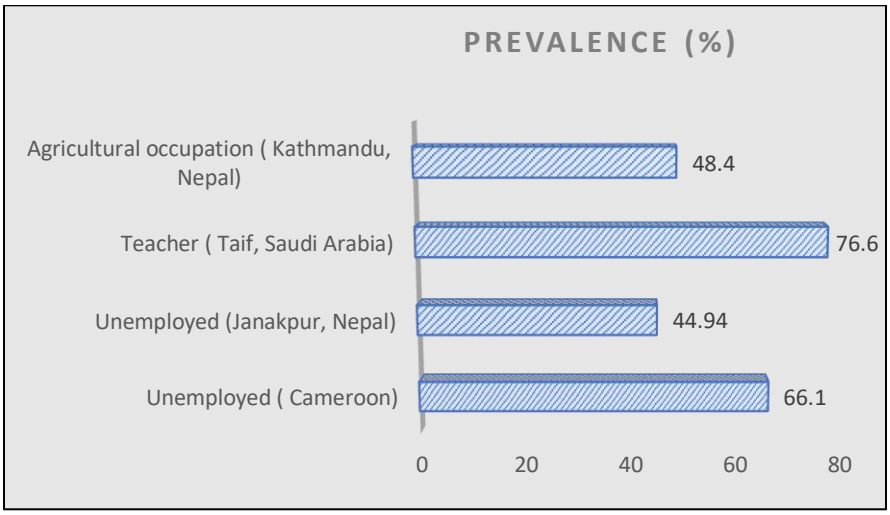

Figure 3: Prevalence of VVC according to employment status

Illiterate women showed highest prevalence (68%) in Sana'a, Yemen whereas patients with university education had 39.7% prevalence (Al-Rukeimi et al., 2020). In Janakpur, Nepal (Yadav & Prakash, 2016) and Southwestern Nigeria (Olowe et al., 2014) pregnant women with no education had 35.5% and 47.6% prevalence respectively. Pregnant women with primary education had been observed to show highest prevalence (37.5%) in Lebanon (Ghaddar et al., 2019).Similar result was found in Maroua, Cameroon with 50% prevalence in the group with primary education (Toua et al., 2013). The difference in the prevalence rate among the illiterate and the educated may be explained by the improvement in personal hygiene and/or the economic situation resulting from education (Al-Rukeimi et al., 2020). Figure 4 represents these data.

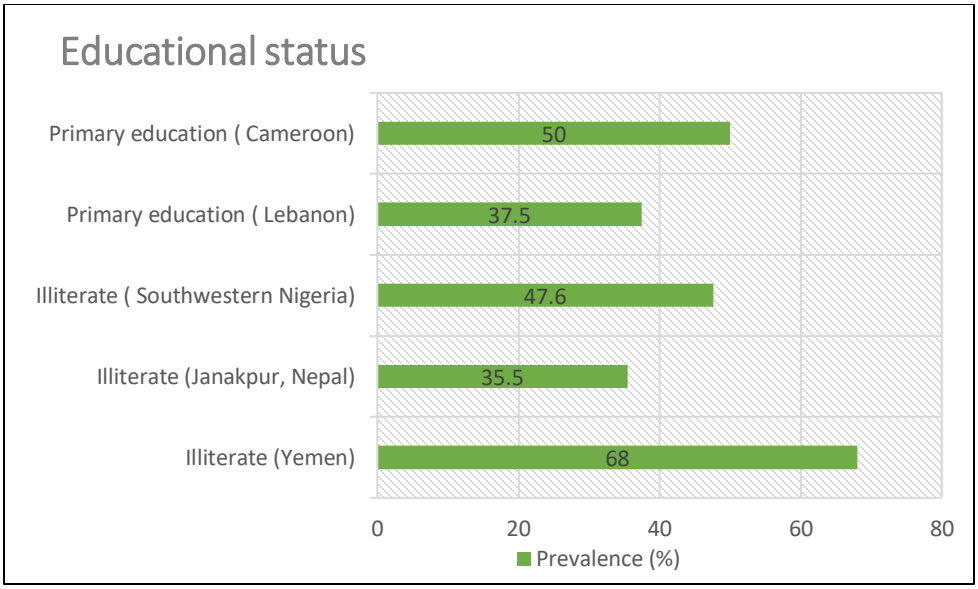

Figure 4: Prevalence of VVC according to educational status

However, no significant difference was found in the prevalence rate of VVC between highly educated women and women with tertiary education (Okonkwo & Umeanaeto, 2011).

In Figure 5, occurrence of VVC according to parity and gravida in pregnant women has been showed. Multi-gravidae (61.5%) mothers are found to have high rate of *Candida* colonization compared to primigravidae (38.5%) (Tsega & Mekonnen, 2019). Kanagal (2014) and Nnadi & Singh (2017) also had found highest prevalence of VVC that is 70% and 70.1% respectively in multi-gravidae women. Women with multipara of parity had 61.8% prevalence which was higher than the prevalence in pauciparous (54.4%) or nulliparous women (38.5%) (Al-Rukeimi et al., 2020). In Kathmandu, Nepal women in their 3rd pregnancy had the highest prevalence (52.6%) among the study participants; this result is in consistent with the previous results (Shrestha et al., 2011). But, contrariwise, Okonkwo & Umeanaeto (2011) found out that the proportion of VVC decreased with parity and the described possible reason for this was the experience that women gathered relating to pregnancy and infections while giving birth to multiple babies.

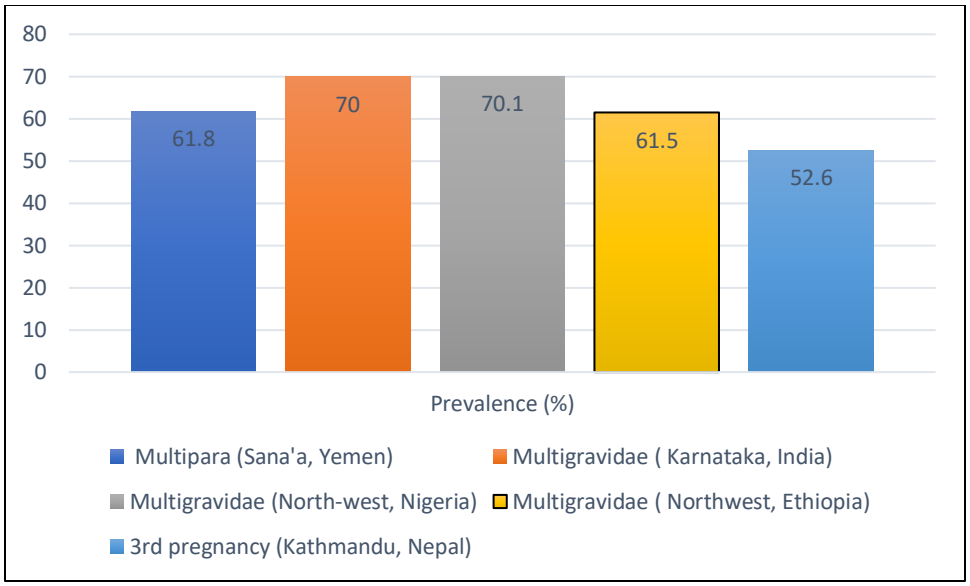

Figure 5: Prevalence of VVC according to parity and gravida

Chapter 4

Risk factors of VVC during pregnancy

Pregnancy has been listed as a risk factor because vagina becomes more sensitive during that time which facilitates infections to occur more frequently (Yadav & Prakash, 2016). The role of pregnancy has been correlated positively with the occurrence of VVC (Mtibaa et al., 2017).The expression of symptomatic VVC during pregnancy depends on some factors like clinical, behavioral and demographical (Aguin & Sobel, 2015). Some host-related factors such as genetic predisposition, uncontrolled DM, behavioral factors (e.g., antibiotic use, contraceptive use) and conditions with high reproductive hormone levels during pregnancy have also been described to be associated with VVC (Jack D. Sobel, 2007).

4.1 Pregnancy - related factors

During pregnancy, several factors related to physiologic changes in pregnant women such as weakened immune system; elevated level of reproductive hormones, glycogen deposition; low vaginal pH; decreased cell mediated immunity have been addressed as risk factors associated with higher risk of VVC in multiple literature.

4.1.1 Weakened immune system

Pregnant women are more prone to infections due to the weakened immune system (Ghaddar et al., 2019). Excess stress had been described as a possible reason for this (Al-Aali, 2013; Edrees et al., 2020). Emotional stress gets increased as a woman is expecting a child which results in the suppression of the immune system and the weakened immune system ultimately steps up the

overgrowth of *Candida* spp. and to become pathogenic (Nelson et al., 2013; Yadav & Prakash, 2016).

4.1.2 Increased level of reproductive hormones

With the progression of pregnancy, hormone levels change drastically and are notably higher than any other time (Jamieson, 2014). During pregnancy, elevated secretion of sex hormones both progesterone and estrogen had been found to favor the formation of infection (Yadav & Prakash, 2016). High level of progesterone is found responsible to cause a change in the vaginal epithelium allowing the implantation of *Candida* yeasts in the vagina (Mtibaa et al., 2017). Along with that, progesterone possesses inhibitory effects on the anti-candida activity of neutrophils (Yadav & Prakash, 2016). The healthy balance of microorganisms can get upset by the increased estrogen level, thus enhancing the likelihood of developing a vaginal infection by *Candida* spp. (Edrees et al., 2020). High levels of estrogen has been found to facilitate the adherence of yeast to vaginal mucosal epithelial cells (Jack D. Sobel, 2007). In addition, estrogen promotes growth, multiplication , hyphal formation (Guzel et al., 2011), and enzyme elaboration such as secreted aspartyl proteinase and phospholipases which increase colonization (Aguin & Sobel, 2015). Moreover, high level of estrogen has been found to reduce immunoglobulins in vaginal secretions as well as to decrease the ability of the epithelial cells to suppress the growth of *Candida albicans* leading to the increased vulnerability to vaginitis during pregnancy (Yadav & Prakash, 2016).

4.1.3 High amount of glycogen deposition

Both progesterone and estrogen has been found to provide an increase amount of glycogen in the vaginal tissue (Babić & Hukić, 2010; Mtibaa et al., 2017). This high level of glycogen deposition provides a good source of carbon which favors the growth and germination of *Candida* spp. on the

wall of the vagina (Babić & Hukić, 2010). Thus, it may have a role in the increased susceptibility of pregnant women to VVC by giving a favorable room for *Candida* enhancement.

4.1.4 Decreased level of pH

Normally, the vaginal pH is maintained at 4.0-4.5 and this level of acidic environment prevents the establishment of many vaginal pathogen (Okonkwo & Umeanaeto, 2011). Yadav & Prakash (2016) stated that any physiological change affecting both beneficial and harmful vaginal microorganisms, alter the acidity of the vagina that reduce its pH to 5.0-6.5, this would thereby enhance the establishment of pathogenic organisms such as *Candida*. Increased level of progesterone during pregnancy has been shown to decrease the vaginal pH thus favoring a suitable environment for *Candida* yeast overgrowth (Mtibaa et al., 2017).

4.1.5 Decreased cell-mediated immunity

During pregnancy, the altered severity of and susceptibility to infectious diseases might be due to the immunologic alterations at that time. The interplay between reproductive hormones and the immune system is complex and multifactorial (Jamieson, 2014). Cell-mediated immunity is important during pregnancy for altered responses to infections (Aguin & Sobel, 2015). According to REED (1992), estrogen enriched states as in the last trimester of pregnancy has been involved in the suppression of the cell-mediated immunity. Progesterone has been found to alter the balance between Th1 and Th2 responses (Aguin & Sobel, 2015) and suppress the maternal immune response (Jamieson, 2014). As gestation advances, estradiol levels can rise as much as 500-fold in the maternal serum (Pazos et al., 2012) and high estradiol concentrations have been found to augment CD4+ type 2 helper T-cell (Th2) responses and humoral immunity (Straub, 2007). Along with that, levels of cytokines increase during pregnancy which stimulate phagocytic cell recruitment or activity (Pazos et al., 2012) . A recent theory had proposed a shift from Th1 to Th2

immunity during pregnancy (Wegmann et al., 1993). Th2 cells decreases cell-mediated immunity by inducing B lymphocytes, increasing antibody production, and suppressing the cytotoxic T-lymphocyte response (Jamieson,2014).

As pregnancy progresses, there is evidence that aspects of innate immunity (phagocytic activity, α-defensin levels, and numbers of monocytes, neutrophils, and dendritic cells) are increased specially in the second and third trimester (Jamieson, 2014) whereas the number of CD3+ T lymphocytes (both CD4+ and CD8+) in blood is decreased (Pazos et al., 2012). This decrease in the numbers and activity of CD4+ cells, CD8+ cells, T-cells and natural killer cells could affect antifungal responses during pregnancy and delay clearance of the offending microorganism (Jamieson, 2014).

4.1.6 Gestation period

Several studies had linked the trimester of pregnancy with the vulnerability of pregnant women to VVC. Okonkwo & Umeanaeto (2011) stated that the vulnerability of pregnant mother to infection increases with the progression of pregnancy, hence the highest prevalence in the third trimester. According to Nelson et al. (2013), increased level of estrogen and corticoids in the 3rd trimester decreases the vaginal defense mechanism against such opportunistic fungus. Along with that, the repetitive vaginal and pelvic examination, reduction in hygiene status such as failure to wash undies and pelvic areas due to fatigue or the tummy size of the pregnant mothers could encourage vaginal infection and pre dispose them to greater chances of VVC in the last trimester of pregnancy (Okonkwo & Umeanaeto, 2011). Guzel et al. (2011) had found an increase in the prevalence with gestation week which is in consistent with the previously mentioned reasons whereas Masri et al. (2015) found pregnant women in their 1st and 2nd trimester to higher risk of getting VVC which is contradictory. However, third trimester of pregnancy had been statistically insignificant with

higher occurrence of VVC in multiple studies (Waikhom et al., 2020; Sangaré et al., 2018; Nnadi & Singh, 2017; Yadav & Prakash, 2016). Waikhom et al. (2020) and Yadav & Prakash (2016) had excluded pregnant women with any complications such as diabetes, previous preterm labor and those who were on antibiotics which could be a possible reason for finding no relation between VVC and gestaional period. So, the role of gestational period especially the last trimester as a risk factor for vulvovaginal candidiasis during pregnancy is still controversial.

4.2 Clinical factors

Diabetes mellitus, HIV infection, and previous encounter with candidiasis has been discussed in several studies as potential factors contributing to the vaginal colonization during pregnancy.

4.2.1 Diabetes mellitus

Uncontrolled diabetes acts as an predisposing factor to VVC (Mtibaa et al., 2017). Patients with clinical diabetes mellitus have an increased risk of *Candida* infections of the skin and vagina (REED, 1992). In diabetes mellitus, concentrations of glucose get increased in the vaginal secretions (Kinghorn, 1991) which promotes adhesion of *Candida* to epithelial cells, stimulates its development and active expression of virulence factors (Mtibaa et al., 2017). The ability of phagocytosis and elimination of pathogen by neutrophils is limited by hyperglycemia condition (Mtibaa et al., 2017). In addition, hyperglycemia can stimulate a protein production in *Candida* spp. which facilitates yeast adherence as well as destroys phagocytosis by the host (REED, 1992). Hence, pregnant women with diabetes may be more prone to VVC as it enhances the growth of yeasts. Statistically significant association between diabetes and rate of VVC during pregnancy had been found in a study by Masri et al. (2015) which is in accordance with the result found by Kanagal (2014). *C. albicans* was found to be significantly associated with gestational diabetes

(Ghaddar et al., 2020). Nevertheless, several studies did not find any significant statistical relationship between diabetes and VVC during pregnancy (Brandão et al., 2018; Mtibaa et al., 2017; Yadav & Prakash, 2016). Guzel et al. (2011) also found no association of DM with prevalence of candida vaginitis during pregnancy. Brandão et al. (2018) described that the possible reason for this disassociation could be the susceptibility of diabetic positive pregnant women to other infections such as bacterial vaginosis resulting in the reduced risk of VVC because of the genesis of bacterial toxins as well as competition for available micro-nutrients, energy resources and mucosal binding sites.

4.2.2 HIV infection

Immunocompromised women are generally at increased risk of fungal infections and this has been shown in studies conducted earlier where increased vaginal colonization with fungi has caused by a loss of immune-protective mechanisms (Foessleitner et al., 2021). Patients who are immunosuppressed, vaginal candidiasis correlate well with reduced cell-mediated immunity (Mtibaa et al., 2017). Predisposing host factors for example HIV infection and other immunosuppressive diseases play a main role in the development of VVC. Moreover, proteinase activity plays a significant role in the pathogenesis of VVC which gets increased in HIV-positive women, hence makes them susceptible to VVC (Foessleitner et al., 2021). Yet, in several studies there was not any significant statistical correlation between HIV infection and VVC (Tsega & Mekonnen, 2019; Mtibaa et al., 2017; Yadav & Prakash, 2016) whereas Foessleitner et al. (2021) found out a greater than twofold increased risk of VVC in HIV positive pregnant women compared with the HIV negative control group . One probable cause of finding insignificant relationship may be the fact that severely immunocompromised patients in particular, are more likely to develop VVC (Mtibaa et al., 2017).

4.2.3 Past episodes of Candidiasis

Patients with previous history of candidiasis have been considered at a greater risk of developing VVC during pregnancy by some authors. This might be due to the hormonal milieu and suppressed immune system which contributes to the increasing susceptibility. During pregnancy, a large proportion of women with chronic recurrent candidiasis are the ones to be first present with the infection (Yadav & Prakash, 2016). Kanagal (2014) had found 60% of candida positive pregnant women with previous candidiasis and this was statistically significant. On the other hand, Yadav & Prakash (2016) found patients with past history of candidiasis to be statistically insignificant with the occurrence of VVC. Hence, it is difficult to claim previous candidiasis as a reliable risk factor for developing VVC.

4.3 Behavioral factors

Several behavioral characteristics of pregnant women might affect the rate of candida colonization during pregnancy. Behavioral factors such as Use of antibiotics, oral contraceptives, intrauterine device; tight clothing; douching habits and poor personal hygiene; poor dietary habits have been assessed as risk factors of VVC during pregnancy in several studies.

4.3.1 Frequent use of oral contraceptives

Pregnant women who have been using oral contraception are considered as being at an increased risk of developing vulvovaginal candidiasis (REED, 1992). Oral contraceptives cause many changes in the vaginal environment that might be associated with the decreased ability to resist Candida infection. Usage of high dose contraceptive pills (75-150 µg of mestranol) has showed to affect glucose tolerance over a short period of time which may in turn promote Candida adhesion or virulence by effecting the carbohydrate source in the vaginal epithelial cells. In addition, oral

contraceptives have been found to be associated with immunological changes including the elevation of antibody in cervical mucous and in the sera; and probably the depression of T-lymphocyte proliferation (REED, 1992) . Furthermore, most oral contraceptives have been found to contain estrogen and progesterone which creates an 'estrogen dominance' by disrupting hormonal balance that results in enhancing Candida growth (Mtibaa et al., 2017). Statistically significant association between prevalence of VVC and previous use of oral contraceptives has been confirmed by Tsega & Mekonnen (2019) and Kanagal (2014). Still, evidences on the risk of VVC in pregnant women using oral contraceptives are conflicting because several studies have found no significant relationship between the prevalence of VVC and use of oral contraceptives (Mtibaa et al., 2017; Yadav & Prakash, 2016; Konadu et al., 2019). This could be due to the use of low dose (REED, 1992) and low estrogen containing (J. D. Sobel et al., 1998) oral contraceptives as they were not considered as significant risk factors for VVC.

4.3.2 Prolonged use of antibiotics

An expanded chance of developing symptomatic VVC in pregnant women following a course of oral antibiotic has been depicted (REED, 1992). Continuous and misuse of drugs leads to the resistance towards drug particularly towards the common antifungal agents utilized for the treatment of vaginal candidiasis (Yadav & Prakash, 2016). Broad spectrum antibiotics use (e.g. tetracycline, ampicillin, cephalosporin) is capable of eliminating *Lactobacillus* spp. in the normal protective bacterial flora of the vagina who prevents germination of Candida by providing a colonization resistance mechanism (Mtibaa et al., 2017). Moreover, antibiotics may play a key role in the overgrowth and increased virulence of the *Candida* spp. by decreasing the prevalence of other competitive bacterial organisms to Candida for substrate (REED, 1992). However, published data on this risk factor are conflicting. Some authors have found prolonged antibiotic use to be

significantly associated with the prevalence of VVC during pregnancy (Tsega & Mekonnen, 2019; Kanagal, 2014; Olowe et al., 2014). Others have shown that pregnant mothers who have a history of antibiotic use do not have an increased prevalence of VVC during pregnancy (Brandão et al., 2018; Mtibaa et al., 2017; Yadav & Prakash, 2016; Konadu et al., 2019; Nnadi & Singh, 2017).

4.3.3 Use of Intrauterine device (IUD)

The intrauterine device (IUD) has been considered as another risk factor in the genesis of VVC. It can be elucidated by the adherence and biofilm production of *C. albicans* on the surface of IUD which contributes to colonization, the reduction of antifungal susceptibility and exhaust to the host immunity. In this way, it contributes to the occurrence of recurrent VVC (Mtibaa et al., 2017). Kanagal (2014) found highly significant association of IUD user pregnant mothers with the prevalence of VVC whereas Mtibaa et al. (2017) and Yadav & Prakash (2016) found statistically insignificant correlation between use of IUD device and prevalence of vaginal candidiasis.

4.3.4 Tight and synthetic clothing

In several literature the types of clothing and undergarments worn have been suggested as risk factor for vulvovaginal candidiasis. Al-Aali (2013) had mentioned that the overgrowth of Candida was enhanced by the use of tight nylon underwear. REED (1992) had described possible mechanisms related to this including increased temperature, moisture or direct irritation of the vaginal area. Wearing tight clothes and synthetic underwear appears to increase the local acidity by nourishing friction and maceration, hence increase the fungal infection (Mtibaa et al., 2017). Despite that, the role of this factor in the prevalence of VVC during pregnancy has still been unproved and anecdotal.

4.3.5 Dietary habits

The role of dietary habits in VVC has been suggested as a risk factor because of the change in Candida virulence in response to the increased available sugar substrates (REED, 1992). Altayyar et al. (2016) had mentioned poor dietary habit as a cause of higher prevalence of VVC among pregnant women. REED (1992) explained that patients with VVC were more likely to excrete sugars such as sucrose, arabinose and ribose; and the associated dietary patterns with these sugars were an elevated intake of milk, yogurt, cottage cheese and artificial sweeteners. Reduction in both the rate of VVC and the presence of sugars in urine were reported by less dairy ingestion (REED, 1992). However, data showing strong relation of diet with prevalence of VVC during pregnancy is scarce. Most studies have failed to show the role of dietary excesses or deficiencies in the etiology of sporadic or recurrent vulvovaginal candidiasis (J. D. Sobel et al., 1998).

4.5.6 Douching habits and female hygiene products

The microbial flora of the vagina can be altered by frequent douching with antiseptics; thus exposing it to Candida infection (Toua et al., 2013). Nevertheless, studies have failed to found an association between douching and vulvovaginal candidiasis during pregnancy (J. D. Sobel et al., 1998). Olowe et al. (2014) also had found no association between douching and VVC.

The presence of Candida organism in the vaginal area may get influenced by the types and frequency of use of sanitary products. The possible reasons making susceptible to infection include direct irritation, drying of the mucosal barrier, mucosal tears, and sensitivity to components and perfumes in the products (REED, 1992). Still, there is not enough evidence showing the use of menstrual protection (e.g. sanitary napkins or tampons) to increase risk of vaginal candidiasis among pregnant women (J. D. Sobel et al., 1998).

Chapter 5

Conclusion

Women in their reproductive age experience at least one episode of candidiasis. The rate of Candida colonization has been found to increase during pregnancy particularly in the 3rd trimester. It has become a matter of concern due to the emerging evidences on the association of VVC with increased risk of pregnancy related complications such as low birthweight and premature delivery. In our analysis, the prevalence of VVC among pregnant women across the world varied from lowest 17% to highest 90%. Pregnant women in Asian and African countries have showed highest prevalence of VVC. In this study, reviewed data identified *C. albicans* as the leading causative agent for VVC followed by *C. glabrata*, *C. krusei*, *C. tropicalis.* Prevalence studies have revealed that the rate of Candidiasis varies with age, parity, gestation period and socio- demographic factors.

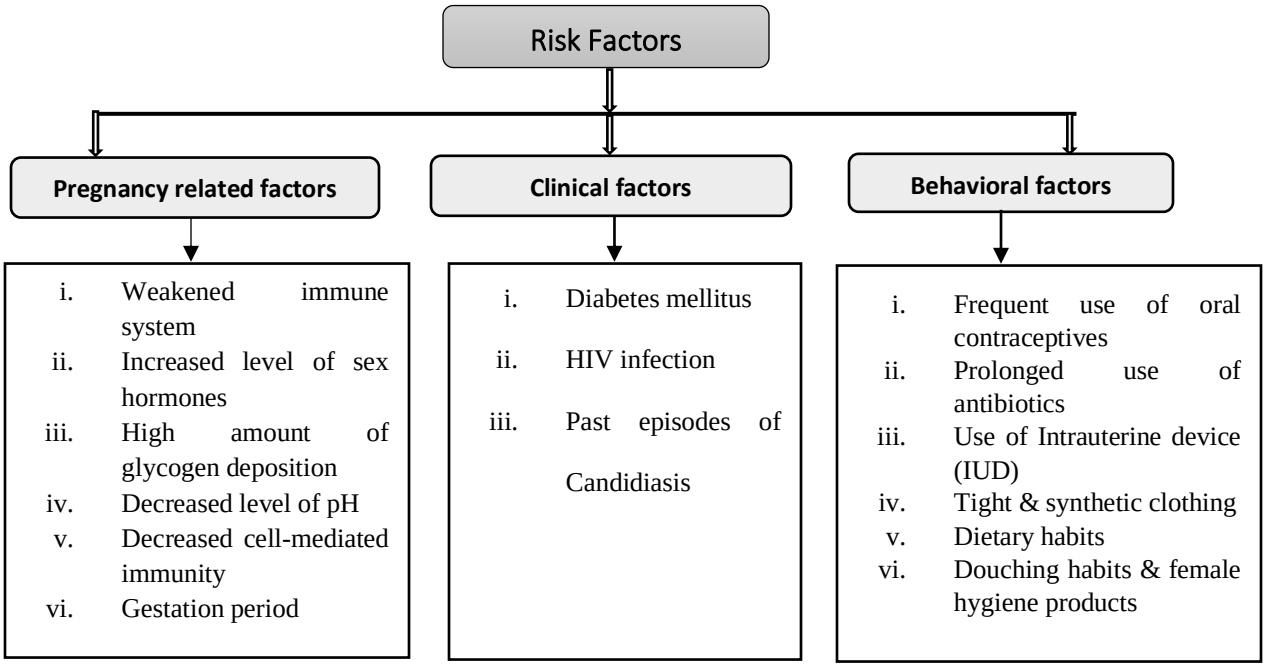

Figure 6: Compilation of different factors associated with VVC during pregnancy.

In figure 6, risk factors of VVC during pregnancy have been summarized. Reviewed literatures have assessed multiple pregnancy related, clinical and behavioral factors as risk factors for developing VVC during pregnancy but not all have been found associated significantly with increased risk of VVC. Also, some studies have found higher prevalence of symptomatic VVC among pregnant women while others have found expression of asymptomatic VVC in greater rate. Increased level of reproductive hormones especially estrogen and progesterone during pregnancy has been found to greatly influence several physiological and immunological changes in pregnant women which further favor Candida colonization in vagina. The impact of elevated level of sex hormones has been summarized in figure 7.

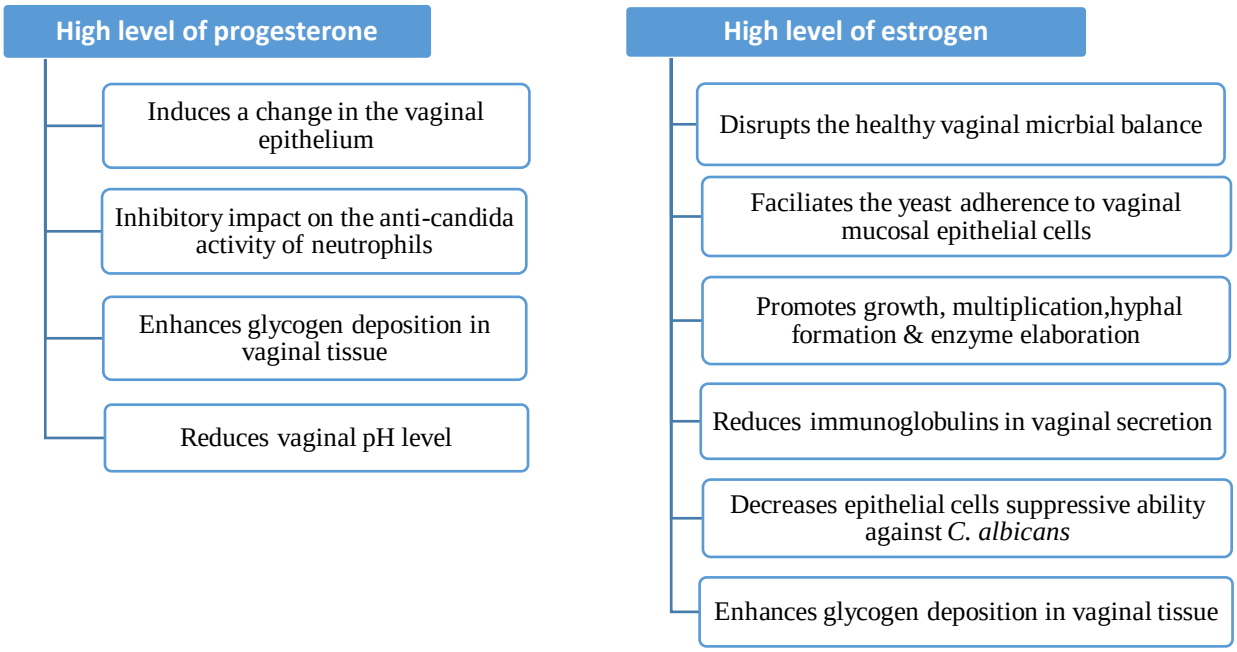

Figure 7: Consequence of elevated level of progesterone and estrogen during pregnancy.

Majority of the time VVC is treated by observing clinical symptoms hence the data on the prevalence rate during pregnancy is not satisfying. Also, the role of associated factors with VVC

is also conflicting. Therefore, it can be said that studies on the prevalence and risk factors of vulvovaginal candidiasis during pregnancy should be carried out more across the world specially in the third world countries to assess the real scenario.

Chapter 6

References

Achkar, J. M., & Fries, B. C. (2010). Candida infections of the genitourinary tract. *Clinical Microbiology Reviews*, *23*(2), 253–273. https://doi.org/10.1128/CMR.00076-09

Aguin, T. J., & Sobel, J. D. (2015). Vulvovaginal Candidiasis in Pregnancy. *Current Infectious Disease Reports*, *17*(6), 15–20. https://doi.org/10.1007/s11908-015-0462-0

Ahmad, A., & Khan, A. U. (2009). Prevalence of Candida species and potential risk factors for vulvovaginal candidiasis in Aligarh, India. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *144*(1), 68–71. https://doi.org/10.1016/j.ejogrb.2008.12.020

Akah, P. A., Nnamani, C. E., & Nnamani, P. O. (2010). Prevalence and treatment outcome of vulvovaginal candidiasis in pregnancy in a rural community in Enugu State , Nigeria. *Journal of Medicine and Medical Sciences*, *1*(November), 447–452.

Al-Aali, K. Y. (2013). Prevalence of Vaginal Candidiasis among Pregnant Women Attending Al-Hada Military Hospital, Western Region, Taif, Saudi Arabia. *International Journal of Science and Research*, *4*(8), 1736–1743. www.ijsr.net

Al-Rukeimi, A. A., Al-Hatami, S. M. M., AL-Danany, D. A., Al-Shamahy, H. A., & Al Rukeimi, R. A. A. (2020). Prevalence and Risk Factors Associated With Vulvovaginal Candidiasis During Pregnancy in Sana'a, Yemen. *Universal Journal of Pharmaceutical Research*, *5*(3), 1–5. https://doi.org/10.22270/ujpr.v5i3.407

Altayyar, I. A., Alsanosi, A. S., & Osman, N. A. (2016). Prevalence of vaginal candidiasis among

pregnant women attending different gynecological clinic at South Libya. *Pelagia Research Library European Journal of Experimental Biology*, *6*(3), 25–29. www.pelagiaresearchlibrary.com

Babić, M., & Hukić, M. (2010). Candida albicans andon-albicans species as etiological agent of vaginitis in pregnant and non-pregnant women. *Bosnian Journal of Basic Medical Sciences*, *10*(1), 89–97. https://doi.org/10.17305/bjbms.2010.2744

Bliss, J. M., Basavegowda, K. P., Watson, W. J., Sheikh, A. U., & Ryan, R. M. (2008). Vertical and horizontal transmission of candida albicans in very low birth weight infants using DNA fingerprinting techniques. *Pediatric Infectious Disease Journal*, *27*(3), 231–235. https://doi.org/10.1097/INF.0b013e31815bb69d

Brandão, L. D. S., Boniek, D., Resende Stoianoff, M. A., da Mata, F. M. R., de Azevedo, P. R. M., Fernandes, J. V., & Andrade, V. S. (2018). Prevalence and antifungal susceptibility of Candida species among pregnant women attending a school maternity at Natal, Brazil. *Letters in Applied Microbiology*, *67*(3), 285–291. https://doi.org/10.1111/lam.13034

Cotch, M. F., Hillier, S. L., Gibbs, R. S., Eschenbach, D. A., Yaffe, S. J., Catz, C. S., Rhoads, G. G., Nugent, R. P., McNellis, D., Klebanoff, M. A., Berendes, H. W., Edelman, R., Blackwelder, W. C., Kaslow, R. A., Reed, G. F., Regan, J. A., Greenberg, E. M., Willams, S., Martin, D. A., … Poole, W. K. (1998). Epidemiology and outcomes associated with moderate to heavy Candida colonization during pregnancy. *American Journal of Obstetrics and Gynecology*, *178*(2), 374–380. https://doi.org/10.1016/S0002-9378(98)80028-8

Dias, L. B., Melhem, M. de S. C., Szeszs, M. W., Filho, J. M., & Hahn, R. C. (2011). Vulvovaginal candidiasis in Mato Grosso, Brazil: Pregnancy status, causative species and drugs tests.

Brazilian Journal of Microbiology, *42*(4), 1300–1307. https://doi.org/10.1590/S1517-83822011000400009

Edrees, W. H., Al-Asbahi, A. A., Al-Shehari, W. A., & Qasem, E. A. (2020). Vulvovaginal Candidiasis Prevalence Among Pregnant Women in Different Hospitals in Ibb, Yemen. *Universal Journal of Pharmaceutical Research*, *5*(4), 1–5. https://doi.org/10.22270/ujpr.v5i4.431

Foessleitner, P., Petricevic, L., Boerger, I., Steiner, I., Kiss, H., Rieger, M. B. A. A., & Farr, V. T. A. (2021). *HIV infection as a risk factor for vaginal dysbiosis , bacterial vaginosis , and candidosis in pregnancy : A matched case-control study*. *December 2020*, 1–8. https://doi.org/10.1111/birt.12526

Ghaddar, N., Anastasiadis, E., Halimeh, R., Ghaddar, A., Dhar, R., Alfouzan, W., Yusef, H., & El Chaar, M. (2020). Prevalence and antifungal susceptibility of Candida albicans causing vaginal discharge among pregnant women in Lebanon. *BMC Infectious Diseases*, *20*(1), 1–9. https://doi.org/10.1186/s12879-019-4736-2

Ghaddar, N., El Roz, A., Ghssein, G., & Ibrahim, J. N. (2019). Emergence of Vulvovaginal Candidiasis among Lebanese Pregnant Women: Prevalence, Risk Factors, and Species Distribution. *Infectious Diseases in Obstetrics and Gynecology*, *2019*. https://doi.org/10.1155/2019/5016810

Gow, N. A. R., & Yadav, B. (2017). Microbe profile: Candida albicans: A shape-changing, opportunistic pathogenic fungus of humans. *Microbiology (United Kingdom)*, *163*(8), 1145–1147. https://doi.org/10.1099/mic.0.000499

Grigoriou, O., Baka, S., Makrakis, E., Hassiakos, D., Kapparos, G., & Kouskouni, E. (2006).

Prevalence of clinical vaginal candidiasis in a university hospital and possible risk factors. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *126*(1), 121–125. https://doi.org/10.1016/j.ejogrb.2005.09.015

Guzel, A. B., Ilkit, M., Burgut, R., Urunsak, I. F., & Ozgunen, F. T. (2011). An Evaluation of Risk Factors in Pregnant Women with Candida Vaginitis and the Diagnostic Value of Simultaneous Vaginal and Rectal Sampling. *Mycopathologia*, *172*(1), 25–36. https://doi.org/10.1007/s11046-011-9392-z

Jamieson, D. J. (2014). *Pregnancy and Infection*. 2211–2218. https://doi.org/10.1056/NEJMra1213566

Kamath, P., Pais, M., & Nayak, M. G. (2013). Original Research Article Risk of vaginal candidiasis among pregnant women. *Int.J.Curr.Microbiol.App.Sci*, *2*(9), 141–146. https://pdfs.semanticscholar.org/f9ac/6c5e90d3178ff5f6f39a9cc56ab26703926d.pdf

Kanagal, D. V. (2014). Prevalence of Vaginal Candidiasis in Pregnancy among Coastal South Indian Women. *Journal of Women's Health, Issues & Care*, *03*(06), 1–3. https://doi.org/10.4172/2325-9795.1000168

Kinghorn, G. R. (1991). Vulvovaginal candidosis. *Journal of Antimicrobial Chemotherapy*, *28*(suppl A), 59–66. https://doi.org/10.1093/jac/28.suppl_A.59

Konadu, D. G., Owusu-Ofori, A., Yidana, Z., Boadu, F., Iddrisu, L. F., Adu-Gyasi, D., Dosoo, D., Awuley, R. L., Owusu-Agyei, S., & Asante, K. P. (2019). Prevalence of vulvovaginal candidiasis, bacterial vaginosis and trichomoniasis in pregnant women attending antenatal clinic in the middle belt of Ghana. *BMC Pregnancy and Childbirth*, *19*(1), 1–10. https://doi.org/10.1186/s12884-019-2488-z

Masri, S. N., Noor, S. M., Mat Nor, L. A., Osman, M., & Rahman, M. M. (2015). Candida isolates from pregnant women and their antifungal susceptibility in a Malaysian tertiary-care hospital. *Pakistan Journal of Medical Sciences*, *31*(3), 658–661. https://doi.org/10.12669/pjms.313.7229

Mendling, W., & Brasch, J. (2012). Guideline vulvovaginal candidosis (2010) of the german society for gynecology and obstetrics, the working group for infections and infectimmunology in gynecology and obstetrics, the german society of dermatology, the board of german dermatologists and the. *Mycoses*, *55*(SUPPL. 3), 1–13. https://doi.org/10.1111/j.1439-0507.2012.02185.x

Mohammadi-Ghalehbin, B., Javanpour Heravi, H., Arzanlou, M., & Sarvi, M. (2017). Prevalence and Antibiotic Resistance Pattern of Candida spp; Isolated From Pregnant Women Referred to Health Centers in Ardabil, Iran. *Journal of Ardabil University of Medical Sciences*, *16*(4), 409-421.

Mølgaard-Nielsen, D., Svanström, H., Melbye, M., Hviid, A., & Pasternak, B. (2016). Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA - Journal of the American Medical Association*, *315*(1), 58–67. https://doi.org/10.1001/jama.2015.17844

Mtibaa, L., Fakhfakh, N., Kallel, A., Belhadj, S., Belhaj Salah, N., Bada, N., & Kallel, K. (2017). Les candidoses vulvovaginales : étiologies, symptômes et facteurs de risque. *Journal de Mycologie Medicale*, *27*(2), 153–158. https://doi.org/10.1016/j.mycmed.2017.01.003

Mucci, M. J., Cuestas, M. L., Landanburu, M. F., & Mujica, M. T. (2017). Prevalence of Candida albicans, Candida dubliniensis and Candida africana in pregnant women suffering from

vulvovaginal candidiasis in Argentina. *Revista Iberoamericana de Micologia*, *34*(2), 72–76. https://doi.org/10.1016/j.riam.2016.09.001

Nelson, M., Wanjiru, W., & Margaret, M. W. (2013). Prevalence of Vaginal Candidiasis and Determination of the Occurrence of Candida Species in Pregnant Women Attending the Antenatal Clinic of Thika District Hospital, Kenya. *Open Journal of Medical Microbiology*, *03*(04), 264–272. https://doi.org/10.4236/ojmm.2013.34040

Nnadi, D. C., & Singh, S. (2017). The prevalence of genital Candida species among pregnant women attending antenatal clinic in a tertiary health center in North-west Nigeria. *Sahel Medical Journal*, *20*(1), 33–37. https://doi.org/10.4103/1118-8561.204333

Okonkwo, N., & Umeanaeto, P. (2011). Prevalence of Vaginal Candidiasis among Pregnant Women in Nnewi Town of Anambra State, Nigeria. *African Research Review*, *4*(4), 539–548. https://doi.org/10.4314/afrrev.v4i4.69250

Olowe, O., Makanjuola, O., Olowe, R., & Adekanle, D. (2014). Prevalence of vulvovaginal candidiasis, trichomoniasis and bacterial vaginosis among pregnant women receiving antenatal care in Southwestern Nigeria. *European Journal of Microbiology and Immunology*, *4*(4), 193–197. https://doi.org/10.1556/eujmi-d-14-00027

Paulitsch, A., Weger, W., Ginter-Hanselmayer, G., Marth, E., & Buzina, W. (2006). A 5-year (2000-2004) epidemiological survey of Candida and non-Candida yeast species causing vulvovaginal candidiasis in Graz, Austria. *Mycoses*, *49*(6), 471–475. https://doi.org/10.1111/j.1439-0507.2006.01284.x

Pazos, M., Sperling, R. S., Moran, T. M., & Kraus, T. A. (2012). *The influence of pregnancy on systemic immunity*. 254–261. https://doi.org/10.1007/s12026-012-8303-9

REED, B. D. (1992). Risk Factors for Candida Vulvovaginitis. *Obstetrical & Gynecological Survey*, *47*(8), 551–560. https://doi.org/10.1097/00006254-199208000-00015

Sangaré, I., Sirima, C., Bamba, S., Zida, A., Cissé, M., Bazié, W. W., Sanou, S., Dao, B., Menan, H., & Guiguemdé, R. T. (2018). Prevalence of vulvovaginal candidiasis in pregnancy at three health centers in Burkina Faso. *Journal de Mycologie Medicale*, *28*(1), 186–192. https://doi.org/10.1016/j.mycmed.2017.08.006

Shrestha, S., Tuladhar, N. R., Basnyat, S., Acharya, G. P., Shrestha, P., & Kumar, P. (2011). Prevalence of vaginitis among pregnant women attending Paropakar Maternity and Women's Hospital, Thapathali, Kathmandu, Nepal. *Nepal Medical College Journal : NMCJ*, *13*(4), 293–296.

Sobel, J. D., Faro, S., Force, R. W., Foxman, B., Ledger, W. J., Nyirjesy, P. R., Reed, B. D., & Summers, P. R. (1998). Vulvovaginal candidiasis: Epidemiologic, diagnostic, and therapeutic considerations. *American Journal of Obstetrics and Gynecology*, *178*(2), 203–211. https://doi.org/10.1016/S0002-9378(98)80001-X

Sobel, Jack D. (2007). Vulvovaginal candidosis. *Lancet*, *369*(9577), 1961–1971. https://doi.org/10.1016/S0140-6736(07)60917-9

Straub, R. H. (2007). *The Complex Role of Estrogens in Inflammation*. *28*(5), 521–574. https://doi.org/10.1210/er.2007-0001

Toua, V., Djaouda, M., Gaké, B., Menye, D. E., Akoachere, E., Tambe, E., Akindoh, V. V., & Njiné, T. (2013). *Prevalence of Vulvovaginal Candidiasis amongst pregnant women in Maroua (Cameroon) and the sensitivity of Candida albicans to extracts of six locally used antifungal plants*. *4*(March), 89–97.

Tsega, A., & Mekonnen, F. (2019). Prevalence, risk factors and antifungal susceptibility pattern of Candida species among pregnant women at Debre Markos Referral Hospital, Northwest Ethiopia. *BMC Pregnancy and Childbirth*, *19*(1), 1–8. https://doi.org/10.1186/s12884-019-2494-1

van Schalkwyk, J., Yudin, M. H., Allen, V., Bouchard, C., Boucher, M., Boucoiran, I., Caddy, S., Castillo, E., Kennedy, V. L., Money, D. M., Murphy, K., Ogilvie, G., & Paquet, C. (2015). Vulvovaginitis: Screening for and Management of Trichomoniasis, Vulvovaginal Candidiasis, and Bacterial Vaginosis. *Journal of Obstetrics and Gynaecology Canada*, *37*(3), 266–274. https://doi.org/10.1016/S1701-2163(15)30316-9

Waikhom, S. D., Afeke, I., Kwawu, G. S., Mbroh, H. K., Osei, G. Y., Louis, B., Deku, J. G., Kasu, E. S., Mensah, P., Agede, C. Y., Dodoo, C., Asiamah, E. A., Tampuori, J., Korbuvi, J., & Opintan, J. A. (2020). Prevalence of vulvovaginal candidiasis among pregnant women in the Ho municipality, Ghana: Species identification and antifungal susceptibility of Candida isolates. *BMC Pregnancy and Childbirth*, *20*(1), 1–14. https://doi.org/10.1186/s12884-020-02963-3

Wegmann, T. G., Lin, H., Guilbert, L., & Mosmann, T. R. (1993). Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? In *Immunology Today* (Vol. 14, Issue 7, pp. 353–356). Elsevier Current Trends. https://doi.org/10.1016/0167-5699(93)90235-D

Yadav, K., & Prakash, S. (2016). Prevalence of vulvovaginal candidiasis in pregnancy. *Global Journal of Medicine and Medical Sciences*, *4*(1), 108–116. https://www.researchgate.net/publication/309572378