ORIGINAL ARTICLE

VULVOVAGINAL CANDIDIASIS AFTER GYNECOLOGICAL SURGERIES AND ADVERSE PREGNANCY OUTCOME IN UKRAINE: A MULTICENTRE STUDY

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ABSTRACT

The aim: To investigate the epidemiology and microbiology of vulvovaginal candidiasis (VVC) after gynecological surgeries, and adverse pregnancy outcomes in Ukraine.

Materials and methods: Multicenter prospective cohort study was conducted from January 2020 to December 2022 and recruited pregnant and non-pregnant women aged 15–65 years who had sought medical help for vaginal dysbiosis the seven medical clinic from five regions of Ukraine.

Results: Between 2020 and 2022, 2,341 women were followed in gynecological practices, and 1,056 (41.5%) women were diagnosed with VVC during the same period. Of the total VVC cases, 31.9% were in non-pregnant and 68.1% in pregnant women. The use of antibiotics (OR=3.48), use hormonal contraceptives (OR=2.75) and pregnancy (OR=1.13) were associated with an increase in the risk of VVC diagnosis. Diabetes mellitus (OR=0.44) were additional risk factors. The most common pathogen of VVC was *C. albicans, Nakaseomyces glabratus (C. glabrata),* followed by *Pichia kudriavzevii (C. krusei), C. parapsilosis, C. tropicalis, C. kefyr, C. guilliermondii, C. lusitaniae,* and *C. rugosa.* We found no significant difference in adverse pregnancy outcomes between *Candida*-positive and Candida-negative women.

Conclusions: Vulvovaginal candidiasis after gynecological surgeries in Ukraine is a common medical problem in women that is associated with significant morbidity, and hence frequent medical visits. High prevalence rate of vulvovaginal candidiasis in the present study warrants, the importance of conducting *continuous* epidemiological surveys to measure changes in species distribution from *C. albicans* to non-albicans *Candida* species in Ukraine.

KEY WORDS: Prevalence, vulvovaginal candidiasis, responsible pathogens, risk factors, adverse pregnancy outcomes, Ukraine

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INTRODUCTION

Vulvovaginal Candidiasis (VVC) affects millions of women every year and has been considered an important public health problem. Although not associated with mortality, the morbidity associated with VVC makes it a major cause of mental distress, causing pain, great discomfort, altered self-esteem, anxiety, impairing work performance and interfering with sexual and affective relations. Despite therapeutic advances, VVC remains a common problem worldwide, affecting all strata of society [1].

According to literature, 75 % of all women will experience at least one episode of VVC in their lives. Between 40 % and 50 % of initially infected women will experience a second episode. In Europe VVC is one of the most common causes of vaginitis, and in the United States, it is the second most frequent cause of infection after bacterial vaginosis [2,3]. Literature evidence regarding VVC reports highlighted that this disease it is the second most common infection of the vulvovaginal area of symptomatic women accounting for about 17% to 42% [4-6]. Vulvovaginal yeast infections in pregnancy are common and can cause extensive inflammation, which could contribute to adverse pregnancy outcomes [7].

Candidiasis is an infection caused by a yeast (a type of fungus) called *Candida*. *Candida* normally lives on skin

and inside the body such as in the mouth, throat, gut, and vagina, without causing any problems. *Candida* can cause an infection if conditions change inside the vagina to encourage its growth. The common term for candidiasis in the vagina is a vaginal yeast infection. Other names for this infection are vaginal candidiasis, vulvovaginal candidiasis, or candidal vaginitis.

Healthcare providers usually diagnose vaginal candidiasis by taking a small sample of vaginal discharge. They examine the sample under a microscope in the medical office or send it to a laboratory for a fungal culture. However, a positive fungal culture does not always mean that *Candida* is causing symptoms. Some women can have *Candida* in the vagina without having any symptoms. Vaginal candidiasis is often mild. About 20% of women normally have *Candida* in the vagina without having any symptoms [2].

Analysis of previous studies showed that understanding of anti-*candida* host defence mechanisms in the vagina has developed slowly and, despite a growing list of recognised risk factors, a fundamental grasp of pathogenic mechanisms continues to elude us. The absence of rapid, simple, and inexpensive diagnostic tests continues to result in both overdiagnosis and underdiagnosis of VVC. Currently, VVC in Ukraine is routinely diagnosed by sign and symptom and is not confirmed with laboratory investigation when necessary. As a result, the spectrum of yeasts implicated in causing VVC, their drug susceptibility profile is not known in the country. In Ukraine, similar studies focused on VVC have not been carried out.

THE AIM

The aim of this study was to investigate the epidemiology and microbiology of VVC after gynecological surgeries, and adverse pregnancy outcomes in Ukraine.

MATERIALS AND METHODS

DESIGN, SETTINGS AND STUDY PARTICIPANTS

Multicenter prospective cohort study was conducted from January 2020 to December 2022 and recruited pregnant and non-pregnant women aged 15–65 years who had sought medical help for vaginal dysbiosis the seven medical clinic from five regions of Ukraine. The study population included women who had history of surgery for gynecological disease. All pregnant women in any trimester who visited the visited the antenatal clinics were interviewed one-on-one and those that gave consent to be part of the study were enrolled. Exclusion criteria included, Chlamydial infections, Syphilis or other sexually transmitted bacterial infections, had bacterial and aerobic vaginosis. Pregnant women who had any pregnancy related complications (diabetes, bleeding per vagina, hypertension) were excluded in the study. Pregnant women were enrolled once to avoid repetition.

DEFINITION OF VULVOVAGINAL CANDIDIASIS

Symptomatic vulvovaginal candidiasis was defined as the presence of clinical presentations and the presence of yeast-liked cells in direct Gram smear with positive culture.

DEFINITION ADVERSE PREGNANCY OUTCOME

Relevant adverse pregnancy outcomes were based on the core outcome set for preterm birth (PTB) research and cross-checked with other core outcome sets in women's and newborn's health. The main outcomes were as follows: PTB, defined as birth at <37 weeks' gestation; spontaneous PTB, defined as birth at <37 weeks' gestation after spontaneous onset of labor or after Preterm prelabor rupture of membranes (pPROM); small for gestational age, defined as birthweight below the 10th percentile for gestational age; pPROM, defined as preterm prelabor rupture of membranes at <37 weeks' gestation; and neonatal death, defined as death during the first 28 days of life. Additional outcomes were as follows: late pregnancy loss, defined as birth between 20- and 24-weeks' gestation; early pregnancy loss, defined as spontaneous demise of pregnancy at <20 weeks' gestation; prelabor rupture of membranes (PROM), defined as rupture of membranes before the onset of labor; birthweight; maternal mortality; maternal morbidity; and neonatal morbidity. Because of the lack of consensus in defining stillbirth, all definitions used for stillbirth were included.

DATA COLLECTION

Information regarding participants' socio-demographics (age, educational level, marital status, trimester in pregnancy) and microbiological data, parity, history of surgical procedure, preoperative and postoperative antibiotic use, complications, and clinical presentations were extracted from participants' ambulatory medical records and relevant hospital records medical records. Information that was not readily available in the medical records were collected using structured questionnaire

Table I. Characteristics study participants (n=2341) with a diagnosis of vulvovaginal candidiasis (VVC) and without VVC in Ukraine, 2020-2022

Variable	Number of women (n=2341)	Vulvovaginal candidiasis		P value
		Yes (n=1056)	No (n=1285)	
Age (years), n (%)				0,062
<18	236	155 (14.7)	81 (6.3)	
18-25	547	411 (38.9)	136 (10.6)	
26-30	712	211 (20.0)	501 (39.0)	
31-35	378	55 (5.2)	323 (25.1)	
36-40	214	86 (8.1)	128 (10.0)	
41-50	189	94 (8.9)	95 (7.4)	
51-60	47	35 (3.3)	12 (0.9)	
>60	18	9 (0.9)	9 (0.7)	
Marital status, n (%)				0.052
Married	786	153 (14.5)	633 (49.3)	
Unmarried	1023	601 (56.9)	422 (32.8)	
Divorced	532	302 (28.6)	230 (17.9)	
Education level, n (%)				0.083
Secondary school	1,243	331 (31.3)	912 (71.0)	
College	481	284 (26.9)	197 (15.3)	
High	617	441 (41.8)	176 (13.7)	
Smoking habits, n (%)	2,296	1,029 (97.4)	1,267 (98.6)	0.362
Alcohol consumption, n (%)	1,535	659 (62.4)	876 (68.2)	0.128
Place of residence, n (%)				0.311
Urban	1,467	659 (62.4)	808 (62.9)	
Rural	874	397 (37.6)	477 (37.1)	
Pregnant status, n (%)				<0.001
Non-pregnant	1,507	337 (31.9)	1,170 (91.1)	
Pregnant	834	719 (68.1)	115 (8.9)	
Multifetal pregnancy, n (%)	436	37 (3.5)	399 (31.0)	0.39
Use hormonal contraceptives, n (%)	756	563 (74.5)	193 (25.5)	<0.001
Weakened immune system (steroid use), n (%)	258	189 (73.3)	69 (26.7)	<0.001
Antibiotic use, n (%)				<0.001
Preoperative antibiotics not given	327	25 (7.6)	302 (92.4)	
Preoperative antibiotics given	921	199 (21.6)	722 (78.4)	
Long-term use of antibiotics	518	364 (70.3)	154 (29.7)	
History of diabetes mellitus, n (%)	168	117 (69.6)	51 (30.4)	0,002
History of adverse pregnancy outcomes, n (%)				0.125
Preterm birth (PTB)	131	19 (14.5)	112 (85.5)	
Spontaneous PTB	127	49 (38.6)	78 (61.4)	
Small for gestational age	211	42 (19.9)	169 (80.1)	
Preterm prelabor rupture of membranes	138	34 (24.6)	104 (75.4)	
Late pregnancy loss	109	18 (16.5)	91 (83.5)	
Early pregnancy loss	98	21 (21.4)	77 (78.6)	
Prelabor rupture of membranes	132	34 (25.8)	98 (74.2)	
Low birth weight	219	26 (11.9)	193 (88.1)	

Table II. Risk factors for VVC in study participants in Ukraine, 2020-2022

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	0.972 (0,944-1.004)	0.062		
Antibionic use	3.476 (2.226-5.427)	<0.001	2.506 (1.536-4.083)	<0.001
Use hormonal contraceptives	2.754 (1.743-4.355)	<0.001	2,616 (1,638-4,174)	<0.001
Pregnancy	1.132 (1.092-1.172)	<0.001	1.142 (1.098-1.185)	<0.001
Diabetes mellitus	0.438 (0.257-0.746)	0.002	0.428 (0.248-0.738)	0.002

OR, Odds Ratio; CI, Confidence Interval.

Table III. Distribution of *Candida* isolates from 2341 patients with vulvovaginal candidiasis (VVC) in Ukraine, 2020-2022

Species of *Candida*	2020 (n=754)		2021 (n=770)		2022 (n=814)		Total (n=2341)		Trend (↑↓)
	n	%	n	%	n	%	n	%	
C. albicans	591	78.4	609	79.1	627	77.0	1827	78.0	↓
Nakaseomyces glabratus (C. glabrata)	35	4.6	41	5.3	43	5.3	119	5.1	↑
Pichia kudriavzevii (C. krusei)	33	4.4	27	3.5	43	5.3	103	4.4	↑
C. parapsilosis	29	3.8	21	2.7	22	2.7	72	3.1	↓
C. tropicalis	17	2.3	23	3.0	29	3.6	69	2.9	↑
C. kefyr	20	2.7	20	2.6	20	2.5	63	2.7	↓
C. guillieromondii	13	1.7	10	1.3	10	1.2	33	1.4	↓
C. lusitaniae	8	1.1	12	1.6	6	0.7	26	1.1	↓
C. rugosa	6	0.8	4	0.5	7	0.9	17	0.7	↑
C. famata	2	0.3	3	0.4	7	0.9	12	0.5	↑

administered to participants of the study. All women were assigned study identification numbers (IDs) which were used throughout the study. The IDs were generated by using the initials of the hospital where participants were enrolled and a chronological number according to how the patients were recruited.

ETHICS

The study received ethics approval from the Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. The present study was performed in line with the principles of the Declaration of Helsinki.

MICROBIOLOGICAL ANALYSIS

After detailed explanation of the sampling procedure to the participants, two high vaginal swabs were obtained by a Gynecologist/trained midwife from each participant using sterile swab sticks. Specimens were taken from the posterior fornix of the vagina with sterile swabs and transported to the microbiology laboratory for further processing. Identification to the species level was performed by MALDI-TOF MS (Bruker Dalto nics) and bacterial strains by Vitek 2 automated system (BioMérieux). For quality control, *C. albicans* (ATCC 10231) was used as reference strain and tested simultaneously with the clinical isolates.

STATISTICAL ANALYSIS

All the analysis were carried out using SAS 9.4 (SAS Institute, Cary, NC, USA). The prevalence of VVC, defined as the proportion of women diagnosed with VVC (denominator: all women who visited the gynecological practices), was analyzed. Categorical data variables were statistically described in the form of frequencies and percentages while continuous data variables were summarized as mean (Standard Deviation). The association between categorical variables were done using chi-square test. The association between VVC diagnosis and the predefined variables was studied using a bivariate analysis and multivariate logistic regression model. P-value less than 0.05 was considered significant.

RESULTS

PREVALENCE OF VVC

During the study period (2020-2022), 1056 of 2341 women's undergoing gynecologic surgery were found to have Vulvovaginal Candidiasis (VVC). The prevalence

of VVC among study participants was 45.1% (95% CI: 44.1–46.1, $p < 0.001$). Of the total VVC cases, 31.9% were in non-pregnant and 68.1% in pregnant women. The highest prevalence rates of VVC were found in the age groups of 18-25 years (38.9%), 26-30 years (30.0%), and <18 years (14.7%), respectively. Demographic and clinical characteristics of study participants with a diagnosis of vulvovaginal candidiasis (VVC) and without VVC are shown in Table I.

RISK FACTORS FOR VVC

The results of the multivariate logistic regression model are displayed in Table II. The use of antibiotics (OR=3.48), use hormonal contraceptives (OR=2.75) and pregnancy (OR=1.13) were associated with an increase in the risk of VVC diagnosis. Diabetes mellitus (OR=0.44) were additional risk factors.

RESPONSIBLE PATHOGENS

In this study after microbiological analyzes 2341 isolates were recovered from the clinical samples. Assessing the prevalence of the identified subtypes, the predominance of *C. albicans* species was found (78.0%), compared to non-albicans *Candida* species (22.0%). The most common non-albicans species were *Nakaseomyces glabratus (C. glabrata)* (5.1%) followed by *Pichia kudriavzevii (C. krusei)* (4.4 %), *C. parapsilosis* (3.1%), *C. tropicalis* (2.9%), *C. kefyr* (2.7 %), *C. guillieromondii* (1.4%), *C. lusitaniae* (1.1%), *C. rugosa* (0.7%) and other species (n=12; 0.5 %). Of the total number of 2341 *Candida* isolates, 1325 (56.6 %) showed bacterial associations. The most common microbial association was *C. albicans* and *S.aureus* - 127 combinations (26.6 %), followed by *C. albicans* and *E.coli* - 99 combinations (20.8 %). Bacterial associations with non-albicans *Candida* species or recorded less frequently. Distribution of *Candida* isolates from patients with VVC during study period (2020-2022) in Ukraine showed in table III.

ADVERSE PREGNANCY OUTCOMES

In this study we found no significant difference in preterm birth (PTB) rate, spontaneous PTB, small for gestational age, preterm prelabor rupture of membranes (pPROM), late pregnancy loss, early pregnancy loss, prelabor rupture of membranes (PROM), and low birth weight between *Candida*-positive and *Candida*-negative women. Characteristics of study participants with history adverse pregnancy outcomes are shown in Table I. Logistic analyses for history adverse pregnancy outcomes among 2,341 women did not reveal any statistically significant associations either.

DISCUSSION

The results of present study provide data as first research in Ukraine that focuses on epidemiology, microbiology, and adverse pregnancy outcomes in Ukraine. Information regarding the prevalence of VVC in Ukraine is not well known.

VVC is not a reportable disease, and therefore, the information on its incidence is incomplete and based on epidemiology studies that are often hampered by inaccuracies of diagnosis and/or the use of non-representative populations. The prevalence of vulvovaginal candidiasis varies from one study to another. Multiple previous studies showed the prevalence rate of VVC among reproductive age women varies between countries and different regions, ranging from 12 to 72% [1, 4-6, 8, 9]. The reasons for such varying prevalence of VVC might be explained the investigation of different geographical locations, profile of the population being studied and period of time in these studies. In this study, the incidence of VVC in Ukraine was found to be 45.1%.

The development of VVC is usually attributed to the disturbance of the balance between *Candida* vaginal colonization and host environment by physiological or nonphysiological changes. The risk factors are believed to be associated with increased rate of VVC including host-related factors such as hyper-estrogenic state (pregnancy, hormone replacement therapy), poorly controlled diabetes, immunodeficiency states, use of antibiotic, treatment with glucocorticoids and genetic predispositions and behavioral factors such as birth control pills, intrauterine device, spermicides and condoms and hygiene habits, tight-fit clothing and sexual behaviour [1]. Other studies have shown that the major risk factors for the development of VVC are lifestyle-related (e.g., frequency of sexual intercourse, contraception, or vaginal douching) [10, 11]. Despite a growing list of recognized risk factors, much remains to be elucidated. In our study the use of antibiotics, use hormonal contraceptives and pregnancy were associated with an increase in the risk of VVC diagnosis, and diabetes mellitus were additional risk factors VVC diagnosis was positively associated with antibiotic prescriptions, prescription of contraceptives, and pregnancy (Table III).

The present study of the total VVC cases, 31.9% were in non-pregnant and 68.1% in pregnant women. Pregnancy and hormone replacement therapy pregnancy has been considered an important risk factor for the development of VVC because several studies report high incidence of the disease in pregnant women. According to literature, VVC caused by *Candida* species, are more common in pregnant women than non-pregnant women [12-14], potentially because

of hormonal and immunological changes that occur during pregnancy [15]. The epidemiologic studies have been consensual in reporting higher prevalence of the disease in pregnant women than in non-pregnant patients, although the incidence varies depending on the locations. The high incidence of VVC in pregnancy has been attributed to the increase of sex hormones secretion in pregnancy. Vulvovaginal candidiasis higher in the last trimester, when levels of hormones are more elevated, even though symptomatic recurrences are common throughout pregnancy [16, 17]. Furthermore, in nonpregnant women the infection is more incident during the luteal phase of the menstrual cycle, which is the phase with the highest hormone.

Candida albicans is the leading cause of vulvovaginal yeast infections; however, other species are becoming relevant in this niche. The spatial distribution of these fungi in the female genital tract remains poorly understood [18]. *Candida* spp. constitute one of the most important genus of opportunistic pathogenic fungi in humans [19, 20], comprising the great majority of isolates obtained from fungal invasive and mucosal infections [20, 21]. Globally, the five species that belong to the genus *Candida*, presently or formerly, that are more commonly associated with candidosis in humans are *C. albicans, Nakaseomyces glabratus* (formerly known as *C. glabrata*), *C. tropicalis, C. parapsilosis,* and *Pichia kudriavzevii* (formerly known as *C. krusei*) [22, 23]. In our study the most common species were *C. albicans, Nakaseomyces glabratus (C. glabrata),* followed *by Pichia kudriavzevii (C. krusei), C. parapsilosis, C. tropicalis, C. kefyr, C. guillieromondii, C. lusitaniae*, and *C. rugosa.*

Present study demonstrates the necessity of identification the *Candida* species responsible for infections in all patients presenting with VVC especially those with recurrent infections. Therefore, identification will influence selection of antifungals and duration of therapy. Simultaneously, compared to previous years, a trend has been observed and that is an increase in the rate of isolation of non-albicans *Candida* species. This phenomenon could be due to the improvement of laboratory diagnostic practices regarding the identification of fungi or a real higher prevalence of these species. The variety of non-albicans *Candida* species involved in human pathology, their rising contribution to fungal infections and the antifungal susceptibility profiles makes their identification at the species level essential for epidemiological investigations, optimizing therapy and patient management.

Recognition that ascending infection leads to adverse pregnancy outcomes has led to a number of studies that have evaluated the treatment of vaginal infections in pregnancy to reduce preterm birth rates. However, the role of candidiasis is relatively unexplored. Some studies suggest an association between vaginal *Candida* colonization and adverse pregnancy outcomes, but the evidence is inconsistent [2, 23-25]. In this study we found no significant difference in adverse pregnancy outcomes between *Candida*-positive and *Candida*-negative women.

STRENGTH AND LIMITATION

To our knowledge, no study addressing of the VVC after gynecological surgeries and risk factors for VVC, and associated adverse pregnancy outcomes. The results of our study provide valuable data as first research in Ukraine and potential for comparison with data from other countries. We recognize that there are some limitations to our study. We were not able to perform analysis on several outcomes, such as late pregnancy loss, spontaneous demise of pregnancy at <20 weeks' gestation, maternal mortality, maternal morbidity, and neonatal morbidity. It is possible that VVC is associated with PTB or another adverse pregnancy outcome with bigger sample size.

CONCLUSIONS

The present study showed that VVC in Ukraine is a common medical problem in women that is associated with substantial discomfort, significant morbidity, and hence frequent medical visits. High prevalence rate of VVC in the present study warrants, the importance of conducting continuous epidemiological surveys to measure changes in species distribution from C. albicans to non-albicans *Candida* species in Ukraine. We did not find strong statistical evidence of an increased risk for preterm birth or eight other adverse perinatal outcomes, in pregnant women with either symptomatic or asymptomatic vulvovaginal VVC. The available evidence is insufficient to make recommendations about testing and treatment of vulvovaginal yeast infection in pregnancy. Future studies should assess vulvovaginal symptoms, yeast organism loads, concomitant vaginal or cervical infections, and microbiota using state-of-the-art diagnostics. Use of molecular diagnostic methods would allow accurate detection and quantification of organism load to determine whether the presence of symptoms is associated with higher organism load, and whether higher organism loads are associated with a higher risk for adverse pregnancy outcomes. VVC cannot be seen in isolation and comprehensive evaluation of the role of concomitant vaginal or cervical infections, or certain microbiota should also be investigated in holistic studies Additional studies on a larger sample and evaluating results of antifungal susceptibility testing are of great importance for optimizing therapy and patient management to fighting VVC with targeted therapy.

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