PREVALENCE OF AEROBIC VAGINITIS AFTER GYNECOLOGICAL SURGERIES AND ASSOCIATED ADVERSE PREGNANCY OUTCOME IN UKRAINE

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ABSTRACT

AIM: To determine prevalence of Aerobic Vaginitis (AV) after gynecologic surgery, risk factors and antimicrobial resistance of responsible pathogens, and adverse pregnancy outcomes in Ukraine.

Materials and Methods: Multicenter retrospective cohort study was conducted from January 2020 to December 2022 in fifteen medical clinics from eight regions of Ukraine. Smears were analyzed using Donders' classification method and Dong's modified AV diagnosis for Gram stains. Definitions of HAIs were adapted from the CDC/NHSN. Antibiotic susceptibility testing of bacteria was determined by Kirby-Bauer disc diffusion test according to the protocol of the EUCAST.

Results: Prevalence of AV among women's undergoing gynecologic surgery in Ukraine was 68.7%. Of the total AV cases, 70.3% were in non-pregnant and 29,7% in pregnant women. The most common pathogen of AV was *Escherichia coli*, followed by *Enterococcus faecalis*, *Streptococcus agalactiae*, *Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Among the *S. aureus* strains, 11,6% of MRSA (Methicillin resistant *S.aureus*) were isolated whereas none of the CoNS were cefoxitin resistant. History of vaginal infection, history of post-operative infection and antibiotic use acted as an important risk factor of AV incidence rate. The presence of AV worsened pregnancy outcomes, by increasing the incidence of preterm birth, the premature rupture of membranes, miscarriage, neonatal jaundice, and neonatal infection.

Conclusions: Aerobic Vaginitis after gynecological surgeries in Ukraine is a common medical problem in women that is associated with significant morbidity, adverse pregnancy outcome, and hence frequent medical visits.

KEY WORDS: Prevalence, aerobic vaginitis, gynecological surgery, antibiotic use, risk factors, pregnancy outcomes, Ukraine.

INTRODUCTION

Female genital tract infections have a high incidence among different age groups and represent an important impact on public health. Vaginitis is one of the most common gynecological diseases in women and may severely affect the quality of life in patients. According to literature, most pathogens may cause the disease, and may take the form of bacterial vaginitis, mixed vaginitis, *Candida vaginitis*, *Mycoplasma vaginitis*, and *Trichomonas vaginitis* [1], the latter having been the most common type in past decades [2]. However, the incidence of *Trichomonas vaginitis* has been decreasing in recent years, while that of bacterial vaginitis has remained stable [3].

Aerobic vaginitis (AV) is an imbalance of the vaginal flora. A decrease in the number of lactobacilli in the vaginal secretion reduces the defense ability and changes the pH value of the vaginal environment, which favors the development of bacterial inflammation [4]. Patients with AV may suffer from abnormal vaginal discharge and vulvae itching and discomfort, which severely affect their quality of life. AV has a complex microbiology. AV is more common than anaerobic vaginitis among all bacterial vaginitis [5], and the pathogens of AV include aerobic Gram-negative and Gram-positive microorganisms [6-8].

According to literature, the occurrence of AV may worsen the outcomes of pregnant women, resulting in more spontaneous preterm delivery and premature rupture of membranes [2,9]. However, previous studies mainly focused on early or late stage pregnancy, and it is hard to understand the incidence of vaginitis across the whole of pregnancy.

The study of risk factors of vaginitis in pregnant women also has important epidemiological and clinical significance. Many studies have explored the risk factors of vaginitis in non-pregnant women, which may differ significantly from those of non-pregnant women, due to hormonal and physiological changes. However, few studies have explored this issue to date, and the risk factors of AV in pregnant women remain unclear. Previous studies have identified the unmarried status, frequent vaginal douching, and long-term use of pregnancy-preventing drugs, and previous history of vaginal infection as the associated risk factors for AV [8-10].

Postoperative infection continues to be significant complications of major gynecologic surgery. The increasing resistance of microorganisms to drugs used in therapy healthcare associated infections (HAI) after gynecological surgeries in female is remarkable, since women report the recurrence of these infections and associated comorbidities. Many studies identified high incidence rates of HAI after hysterectomy for benign gynecological disease, and most cases were caused by pathogens that are resistant to antibiotics [11-14]. Majority of these cases were detected post discharge [11-14]. Few studies have examined the characteristics of aerobic vaginal flora samples in female, and no studies have examined them in women with postoperative infection and adverse pregnancy outcome. In Ukraine, similar studies on AV have not been carried out.

AIM

The aim of this study was to determine prevalence of AV after gynecologic surgery, risk factors and antimicrobial resistance of responsible pathogens, and adverse pregnancy outcomes in Ukraine.

MATERIALS AND METHODS

DESIGN, SETTINGS AND STUDY PARTICIPANTS

We performed a multicenter retrospective cohort study from January 1st, 2020 to December 31st, 2022. Our study included 3,125 women's (pregnant and non-pregnant) reproductive age (15 to 49 years) with symptomatic vaginal discharge, attending the fifteen medical clinic from eight regions of Ukraine. Our study population included women had history of gynecological surgery. All study participants were local residents. Exclusion criteria: Chlamydial infections, Syphilis or other sexually transmitted bacterial infections, patients with diagnosis of bacterial vaginosis, candidiasis and trichomoniasis, participation in a clinical trial using antibiotics or genital microbicides.

DEFINITION

Definitions of HAIs after gynecological surgery were adapted from the Centers for Disease Control and Prevention's National Healthcare Safety Network. Aerobic vaginitis (AV) was diagnosed if smears were deficient in lactobacilli, positive for cocci or coarse bacilli, positive for parabasal epithelial cells, and positive for vaginal leukocytes [15]. We focused on AV, and smears were analyzed using Donders' classification method and Dong's modified AV diagnosis for Gram stains [16, 17]. 'Any AV' was defined as an AV score of 4 or more, with a subclassification of 'light AV' if the score was 4–5, 'moderate AV' if it was between 6–7, and 'severe AV' when it was 8–10.

DATA COLLECTION

We developed a special questionnaire. Following enrolment, the baseline characteristics of patients was collected including age, body mass index, multifetal pregnancy, parity, history of cesarean delivery, microbiological, and clinical data, including invasive procedures, history surgical procedure and post-operative infections, previous hospitalization within one year after the current hospitalization, antibiotics usage (preoperative and postoperative antibiotic use), history of vaginal infection, history of hypertension and diabetes mellitus, level of education, history of smoking, and occupational status. All pregnant women were followed up until 1 month after delivery. Some pregnant outcomes were recorded in this study for further analysis, including delivery mode, preterm birth, premature rupture of membranes, birth weight, Apgar score, neonatal jaundice, neonatal infection, and stillbirth. This study includes interviews, guestionnaires, and examinations medical records. Information was collected at baseline visit. Ambulatory medical records and relevant hospital records were reviewed for the study participants.

ETHICS

Institutional ethical committee clearance was taken. The samples were collected after obtaining informed consent from the patients. They were explained the purpose of the study and the procedures involved.

MICROBIOLOGICAL ANALYSIS

All enrolled participants underwent a gynecological examination, and a sterile cotton swab was used to obtain samples of vaginal discharge. Vaginal swab specimens were collected from females with symptomatic vaginal discharge, attending the medical clinics. Two high vaginal swabs were collected using sterile cotton swabs and were then immediately brought to the laboratory for processing. The first swab was used for Gram stain examination under 400x (for determining AV score) and 1000x magnification (for identification of organism). Smears were analyzed using Donders' classification method and Dong's modified AV diagnosis for Gram stains. Species identification was performed with standard microbial methods. The antibiotic susceptibility of the isolates was tested using the Kirby-Bauer disc diffusion method with Mueller Hinton agar and 5% sheep blood agar for the exigent strains. Thereafter, resistance data were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) -2020 guidelines (http://eucast.org).

STATISTICAL ANALYSIS

In this study for all patients, demographic data, information about pregnancy outcomes, and genital symptoms (AB) were recorded. SPSS 24.0 software was used for data processing and statistical analysis. Both bivariate analysis and multivariate regression analysis were used to evaluate the correlation of different variables. For bivariate analysis, the significance of differences between the two groups was evaluated using the Student T-tests and the Pearson's chi-square χ^2 test. To express any significant difference, estimates with 95% confidence intervals were obtained using regression analysis. A P<0.05 significance level was used for all statistical tests.

RESULTS

PREVALENCE OF POST-OPERATVE AEROBIC VAGINITIS

During the study period, 2147 of 3125 women's undergoing gynecologic surgery were found to have Aerobic Vaginitis (AB). Of the total postoperative AV cases, 70.3% (1509/2147) were in non-pregnant and 29,7% (638/2147) in pregnant women. The prevalence of AV among study participants was 68.7% (95% CI: 67.9–69.5). The differences in age distribution between the vaginal infection and no vaginal infection groups were statistically significant (P < 0.001). Twenty-nine percent of women had normal vaginal flora on microscopy, while 15.3% suffered from severe AV, 32.3% had moderate AV, and 16.9% had mild AV, compared to 0%, 2%, and 10%, respectively, in the normal group (p < 0.0001). Demographic and clinical characteristics of participants are shown in Table 1.

BACTERIAL PATHOGENS AND ANTIMICROBIAL RESISTANCE

In this study of 2256 culture positive samples, 80.8% (1823/2256) samples yielded single organism on culture and 19.23% (433/2256) yielded dual organisms (mixed). The most common pathogen of AV in this study was *Escherichia coli* (28.5%), followed by *Enterococcus faecalis* (17.5%), Group B *Streptococcus* (8.7%), *Staphylococcus aureus* (8.4%), *Enterococcus faecium* (8.2%), *Klebsiella pneumoniae* (7.4%), Coagulase-negative staphylococci (7.1%), *Pseudomonas aeruginosa* (5.9%), *Acinetobacter baumannii* (3.9%), *Lactobacillus* (2.9%), and other pathogens (1.4%). The distribution of bacterial pathogens in pregnant women with AV is summarized in Table 2.

There were 40% AV cases of mixed infections with E. faecalis and E.coli followed by 20% case each of E.coli + P. aeruginosa, S. aureus + E.coli and K. pneumoniae + CoNS. There was a greater predominance of grampositive organisms in this study which seemed to show more resistance to penicillin and ampicillin except for Group B Streptococcus (S. agalactiae), which showed 100% sensitivity. Among the E. faecalis isolates, only 10% of them showed high level resistance to gentamicin. Among the S. aureus strains, 22 cases of MRSA (Methicillin resistant S.aureus) were isolated whereas none of the CoNS were cefoxitin resistant. The gram-positive organisms were maximum sensitive towards β -lactams/ β -lactamase inhibitor combinations, vancomycin and linezolid. The gram-negative isolates were least sensitive to ampicillin but showed moderate sensitivity towards third generation cephalosporin, aminoglycosides and fluoroquinolones but

were highly sensitive to amoxyclav and meropenem. The most effective antibiotics against Pseudomonas aeruginosa were gentamicin, tobramycin and meropenem.

RISK FACTORS OF AEROBIC BAGINITIS AND PREGNANCY OUTCOMES

In this study risk factors of AV among study participants were analyzed using logistic regression as shown in Table 3. Age, history of cesarean delivery, history of vaginal infection, history of post-operative infection, antibiotic use, college education or above, and occupational status showed significant effects on the incidence of AV according to univariable logistic regression. However, after adjustment using multivariable logistic regression, a history of vaginal infection, history of post-operative infection and antibiotic use acted as an important risk factor of AV incidence, and a history of cesarean delivery, college education or above, and occupational status could protect study participants from the incidence of AV.

In this study pregnancy outcomes of women with AV are listed in Table 4. Vaginal delivery took place in 59.4% and 66.5% women in the without AV group and with AV group, respectively, and preterm birth occurred in 79 women (8.1%) in the without AV group and 412 women (19.2%) in the with AV group, showing significant difference (P<0.001). Similarly, premature rupture of membranes occurred in 91 women (9.3%) in the without AV group and 567 women (26.4%) in the with AV group, showing significant difference (P<0.001). Miscarriage occurred in 84 (8.6%) women in the without AV group and 599 women (27.9%) in the with AV group, showing significant difference (P<0.001). Neonatal jaundice was observed in 79 neonates (8.1%) of the without AV group and 318 neonates (14.8%) of the with AV group, showing a significant difference (P=0.007), and neonatal infection was observed in 40 neonates (4.1%) of the without AV group and 177 (8.2%) of the with AV group, also showing a significant difference (P=0.025). Only 11 stillbirth was observed in all enrolled women of both groups.

DISCUSSION

The results of present study provide valuable data as first research in Ukraine that focuses on the prevalence of AV after gynecological surgeries, bacterial pathogens and antimicrobial resistance, risk factors, and its impact on adverse pregnancy outcomes. In our study the prevalence of AV among study participants was 68.7%. Of the total postoperative AV cases, 70.3% were in nonpregnant and 29,7% in pregnant women. According to literature, the frequency of AV varies from 12% to 23.7% in symptomatic women who are not pregnant and 4 to 8% during pregnancy [18].

One of the most controversial issues is that the specific increasing pathogens and specific decreasing *Lactobacillus* species that contribute to AV remain poorly recognized. Based on classical cultivation methods, the most common bacteria related to AV in prior studies were Group B *Streptococcus* (*Streptococcus agalactiae*); *S. aureus; E.*

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Pregnant status, n (%)	0.046
Non-pregnant 1,799 1,509 (70.3) 290 (29.7)	
Pregnant 1,326 638 (29.7) 688 (70.3)	
Multifetal pregnancy, n (%) 43 35 (1.6) 8 (0.8)	0.39
Parity, n (%)	0.283
0 1,947 1,381 (64.3) 566 (57.9)	
1 1,098 719 (33.5) 379 (38.8)	
2 80 47 (2.2) 33 (3.4)	
History of Cesarean delivery, n (%) 629 432 (9.9) 197 (20.1)	0.002
History of vaginal infection, n (%) 577 484 (22.5) 93 (9.5)	< 0.001
History of hypertension, n (%) 77 48 (2.2) 29 (3.0)	0.793
History of diabetes mellitus, n (%) 38 23 (1.1) 15 (1.6)	1.0012
History of post-operative infection, n (%) 2,079 1,883 (87.7) 196 (20.0)	<0.0001
Antibiotic use, n (%)	<0.0001
Preoperative antibiotics not given 903 168 (7.8) 735 (75.2)	
Preoperative antibiotics given 577 466 (21.7) 111 (11.3)	
Post-operative long-term use of antibiotics 1,645 1,513 (70.5) 132 (13.5)	

faecalis; CoNS, such as *S. epidermidis*; and *E. coli* [18-20]. However, cultivation studies on vaginal bacteria from patients with AV exhibited heterogeneous results. We hypothesized that multiple aerobic microorganisms were involved or the causative bacteria were difficult to cultivate by conventional methods. In our study the most common pathogen of AV in this study was *E. coli*, followed by *E. faecalis*, *S. agalactiae*, *S. aureus*, *E. faecium*, *K. pneumoniae*, CoNS, *P. aeruginosa*, *A. baumannii*, *Lactobacillus*, and other pathogens.

Table 2. Distribution of bacterial pathogens in study participants with AV in Ukraine

Organisms	Total no. of isolates	Percentage (%)
Escherichia coli	642	28.5
Enterococcus faecalis	395	17.5
Group B Streptococcus (S. agalactiae)	197	8.7
Staphylococcus aureus	190	8.4
Enterococcus faecium	185	8.2
Klebsiella pneumoniae	167	7.4
Coagulase-negative staphylococci	161	7.1
Pseudomonas aeruginosa	134	5.9
Acinetobacter baumannii	88	3.9
Lactobacillus	65	2.9
Others	32	1.4
Total	2,256	100.0

Table 3. Risk factors of AV in study participants in Ukraine

Variable	Univariable ana	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value	
Age (years)	0,972 (0,944-1.004)	0,072	-		
History of Cesarean delivery	0,438 (0,257-0,746)	0,002	0,428 (0,248-0,738)	0,002	
History of vaginal infection	2,754 (1,743-4,355)	<0,001	2,616 (1,638-4,174)	<0,001	
History of post-operative infection	1.132 (1.092-1.172)	<0,001	1.142 (1.098-1.185)	<0,001	
Antibiotic use	3.476 (2.226-5.427)	<0,001	2.506 (1.536-4.083)	<0,001	
Education of college or above	0,566 (0,387-0,835)	0,004	0,578 (0,388-0,856)	0,006	
Occupational status	0,647 (0,429-0,982)	0,039	0,637 (0,415-0,977)	0,04	

Table 4. Pregnancy outcomes of women with post-operative Aerobic Vaginitis in Ukraine

Variable	Number of women	Aprohic Vaginitic		<i>P</i> value
		Yes (n=182)	No (n=503)	<i>P</i> value
Delivery mode, n (%)				0.095
Vaginal delivery	2,009	1,428 (66.5)	581 (59.4)	
Cesarean section	1,116	719 (33.5)	397 (40.6)	
Preterm birth, n (%)	491	412 (19.2)	79 (8.1)	0.001
Premature rupture of membranes, n (%)	658	567 (26.4)	91 (9.3)	0.001
Miscarriage	683	599 (27.9)	84 (8.6)	0.001
Birth weight, n (%)				0.572
<2500	209	152 (7.1)	57 (5.8)	
2500-4000	2,740	1,864 (86.8)	876 (89.7)	
>4000	176	131 (6.1)	45 (4.6)	
Apgar score, n (%)				0.613
<7	30	24 (1.1)	6 (0.6)	
≥7	3,095	2,123 (98.9)	972 (99.4)	
Neonatal jaundice, n (%)	397	318 (14.80	79 (8.1)	0.007
Neonatal infection, n (%)	217	177 (8.2)	40 (4.1)	0.025
Stillbirth, n (%)	11	11 (0.5)	0 (0)	0.266

Our study looks at the significance of AV, characterized by an increase in the number of resistant aerobic bacteria, including strains of both gram-positive and gram-negative microorganisms. In this study, many patients with AV had a history of post-operative infections associated surgical gynecological procedures. The reported incidence of healthcare-associated infection (HAI) after gynecological surgeries in Ukraine among women ranges from 9,9 to 25% [12-14, 21, 22]. The predominant HAI types were Cervicitis, Pelvic abscess or cellulitis, Salpingitis, Oophoritis, Adnexa uteri, Vaginal cuff infections, Endometritis, and Chorioamnionitis. 93.8% of HAIs were detected post discharge [13]. The most commonly identified pathogen was E. coli, Enterobacter spp., followed by Klebsiella spp., Streptococcus spp., and P. aeruginosa. The overall proportion of extended spectrum beta-lactamase production (ESBL) among Enterobacteriaceae was 17.1% and of methicillinresistance in S. aureus (MRSA) 15.8%. Resistance to thirdgeneration cephalosporins was observed in 13.7% E.coli and 8.5% Klebsiella spp. isolates. Carbapenem resistance was in 9.7% of *P.aeruginosa* strains [13].

Aerobic vaginitis is an imbalance of the vaginal flora and the main characteristic is an abnormal vaginal flora that contains aerobic and intestinal pathogens with varying degrees of vaginal inflammation. Essential treatment should result in the establishment of homeostasis of the vaginal environment where Lactobacilli play a role a charming role. Intensive treatment of AV could be a very important factor in preventing of precancerous lesions and cervical cancer.

The recommended treatment of AV includes a combination of therapy such as: antibacterial (antiseptic and antibiotic), hormonal, non-steroidal anti-inflammatory and/or probiotics, which can be prescribed in the form of local or systemic therapy. There is no generally accepted clinical strategy for the treatment of AV caused by multi-resistant strains Gram-negative and Gram-positive organisms. Therapy should be based on microbiological findings using a topical antibiotic for the infectious agent, a topical steroid to reduce inflammation, and estrogen to treat atrophy.

We in present study determined the risk factors of AV according to multivariable logistic regression and found the most important risk factor to be a history of vaginal infection, history of post-operative infection and antibiotic use. This is consistent with the results of other authors [2, 23]. Previous studies have shown intrauterine device use, external hemorrhoids, long-term antibiotic use, and frequent vaginal douching were independent risk factors for AV [2].

We found that the presence of AV worsened pregnancy outcomes, by increasing the incidence of preterm birth, the premature rupture of membranes, miscarriage, neonatal jaundice, and neonatal infection. Previous studies also confirmed that AV would increase the incidence of neonatal jaundice and neonatal infection [9], and preterm birth and premature rupture of membranes [24]. However, it also found that AV would increase the proportion of neonates with low birth weight. Only 209 neonates with low birth weight were delivered in our study and there was no significant difference between the two groups. After adjustment using multivariable logistic regression, older age, especially older than 40 years, was also seen as an important risk factor of adverse pregnant outcomes, which is similar to the results of a previous study [25].

Our study emphasized on the need to identify the aerobic vaginal pathogens associated with vaginitis especially in reproductive age group women which can go a long way in preventing the adverse outcomes associated with pregnancy and also ensures the necessity to determine the antibiotic sensitivity pattern of the pathogens which can aid in making a suitable therapeutic choice for 'aerobic vaginitis' by considering an antibiotic that is characterized by an intrinsic activity against the majority of bacteria, bactericidal effect and without any interference with the vaginal microbiota.

Finally, this study determined the prevalence and risk factors for AV among pregnant women after gynecological surgeries in Ukraine to generate findings that could guide the design of interventions for prevention of infection and associated poor pregnancy outcomes.

STRENGTH AND LIMITATION

The results of present study provide valuable data as first research in Ukraine that focuses on the prevalence of AV after gynecological surgeries, antimicrobial resistance pathogens, and risk factors for adverse pregnancy outcomes, and potential for comparison with data from other countries. The results of present study provide valuable data as first research focused on AV in Ukraine and potential for comparison with data from other countries.

Limitations: Firstly, as a retrospective study, the types of data that can be collected are relatively limited. Some other data such as the results of serological and immunological examinations could not be obtained, which may affect the final result. Secondly, follow-up and data collection were performed when women attended hospital for prenatal examination and delivery, and some risk factors of AV and adverse pregnancy outcomes that may have existed out of hospital and after delivery could also not be collected. Thirdly, different pathogens of AV were identified in our study, and it is still unclear what effect each of these pathogens has on pregnancy outcomes. Studies focusing on the effect of a single pathogen may improve the quality of future studies.

CONCLUSIONS

Aerobic Vaginitis after gynecological surgeries in Ukraine is a common medical problem in women that is associated with substantial discomfort, significant morbidity, adverse pregnancy outcome (preterm birth, preterm premature rupture of membranes, miscarriage, low birth weight, neonatal and maternal infections), and hence frequent medical visits. Most number of cases of AV are associated with vaginal infections and long-term use of antibiotics to treat post-operative infections. These infections must be identified and treated promptly. Antibiotics used to treat vaginitis must be very selective in order not to kill the beneficial bacteria (*Lactobacilli*) that help in preservation of vaginal health and ecosystem, being one of the probiotic bacteria. Therapy should be based on microbiological findings using a topical antibiotic for the infectious agent, a topical steroid to reduce inflammation, and estrogen to

treat atrophy. The high incidence of AV-associated with postoperative infections highlights, further research is needed to determine the etiology and understand potential causal linkages between AV after gynecological surgeries, and adverse pregnancy outcomes.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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