ORIGINAL ARTICLE

HEALTHCARE-ASSOCIATED TUBO-OVARIAN INFECTIONS IN UKRAINE: RESULTS OF A MULTICENTER STUDY (2020-2022)

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ABSTRACT

The aim: To determine the current prevalence of healthcare-associated tubo-ovarian infections in female and antimicrobial resistance of the responsible pathogens in Ukraine.

Materials and methods: We performed a retrospective multicenter cohort study was based on healthcare-associated infections surveillance data. Definitions of healthcare-associated tubo-ovarian infections were used from the CDC/ NHSN. The susceptibility to antibiotics was determined by disk diffusion method according to the EUCAST.

Results: Among all the 1,528 of women in this study, the prevalence of healthcare-associated tubo-ovarian infections was 31.2%. Of these cases, Salpingitis, Oophoritis, and tubo-ovarian abscess were 47.5%, 34% and 18.5%, respectively. Of all cases tubo-ovarian infections in female, 74.7% were detected after hospital discharge. The predominant pathogens were: *Escherichia coli* (27.7%), *Enterobacter* spp. (12.2%), *Klebsiella pneumoniae* (9.6%), *Staphylococcus aureus* (8.2%), *Pseudomonas aeruginosa* (8.1%), and *Enterococcus faecalis* (7.5%), followed by *Proteus mirabilis* (5.1%), *Streptococcus* spp. (4.5%), *Staphylococcus epidermidis* (4.4%), and *Acinetibacter* spp. (4%). Methicillin-resistance was observed in 16.8% of *S. aureus* (MRSA). No strains *S.aureus* and *E. faecalis* resistant to vancomycin. The overall proportion of extended spectrum beta-lactamases (ESBL) production among *Enterobacteriaceae* was 24.7%. The prevalence of ESBL production among *E. coli* isolates was 28.6% and among *K. pneumoniae* 12.8%. Resistance to third-generation cephalosporins was observed in 14.9% *E.coli* and 11.3% *K. pneumoniae* isolates. Carbapenem resistance was identified in 11.3% of *P.aeruginosa* isolates.

Conclusions: A healthcare-associated tubo-ovarian infections of the female in Ukraine is a common occurrence and many cases are caused by pathogens that are resistant to antibiotics.

KEY WORDS: female infertility, hysterectomy, salpingitis, oophoritis, tubo-ovarian abscess, responsible pathogens, antimicrobial resistance

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INTRODUCTION

Reproductive tract infections (RTI) in female remain a major public health problem and patient safety threat worldwide, causing increased morbidity and mortality in women. In addition, these infections may result in female infertility, ectopic pregnancy and chronic pelvic pain and other disease [1-3]. Prevalence of female RTI varies from country to country and ranges from 1.8% to 48% [4-6]. According to literature, in the United States, 1 million women are diagnosed with RTIs each year and the cost of their treatment is estimated at $ 4.2 billion [7].

It is known that the female genital tract may be affected by ascending infection, either from sexually transmitted infections or vaginal flora, or occasionally from secondary infections from gastrointestinal sources. It results in salpingitis, oophoritis, and/or tubo-ovarian abscess (TOA). These infections are one of the causes of infertility in women of reproductive age [8]. According to the literature, a significant part of salpingitis, oophoritis and / or TOA are detected after gynecological surgery [4, 8]. Despite the introduction into medical practice of new diagnostic technologies for diagnosis and treatment, as well as broad-spectrum antibiotics, the number of healthcare-associated tubo-ovarian infections in female is not decreasing.

In the available literature, there are many studies devoted to female reproductive tract infections as results by ascending infection, either from sexually transmitted infections or vaginal flora, or occasionally from secondary infections from gastrointestinal sources. However, there are a limited number of studies on tubo-overian infections associated with gynecological surgery.

According to literature, one of the reasons for healthcare-associated RTIs is the wide spread of conditionally pathogenic microorganisms in Ukraine that are resistant

to antibiotics [5, 9]. Therefore, the emergence and spread of antimicrobial resistance has become a major public health threat in Ukraine, and the number of infections caused by resistant pathogens causing of RTIs continues to increase [4].

It is known that the antimicrobial resistance creates obstacles for effective prevention and treatment of patients with infections. Every year resistant healthcare-associated infection is becoming more and more pressing for doctors in Ukraine. Microbiological monitoring of the prevalence of etiologic agents of RTIs in female and antimicrobial resistance is necessary to enhance our knowledge of its epidemiology. However, the prevalence of most healthcare-associated RTIs (including tubo-ovarian infections) and antimicrobial resistance of causative agents have not been studies in Ukraine. This was the basis for our study.

THE AIM

The aim of this study was to determine the current prevalence of healthcare-associated tubo-ovarian infections in female and antimicrobial resistance of the responsible pathogens in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

We performed a retrospective multicenter cohort study was based surveillance data for healthcare-associated reproductive tract infections were according to CDC/NHSN methodology. The study was conducted from January 1, 2019 to December 31, 2021 in 11 women's hospitals from 7 regions of Ukraine. The hospitals had 1320 beds. They are similar in terms of medical equipment and staff. All participating hospitals were required to have at least one full-time infection-control professional, a clinical microbiology laboratory.

PARTICIPANTS

Inclusion criteria: This study included 1,528 women's aged 16-55 years admitted to hospitals with the diagnosis of benign gynecological disease and undergoing a laparoscopic hysterectomy procedure. All women were local residents.

Exclusion criteria: current pregnancy; positive serological test for syphilis or other sexually transmitted infections; inflammatory bowel disease or significant renal or hepatic disease; had a history of colitis; neoplasms or haematological malignancy; gynecological surgery within the last month (30 days) prior to admission.

DEFINITIONS

Diagnosis of salpingitis, oophoritis, and/or tubo-ovarian abscess in female was based on criteria from the CDC/NHSN Surveillance Definitions for Specific Types of Infections.

DATA COLLECTION

In this study we analyzed the inpatient data and ambulatory medical records to identify salpingitis, oophoritis, and/or tubo-ovarian abscess in female. We collected the data using structured NHSN Reproductive Tract Infection (REPR) Checklist. Full-text ambulatory medical records and relevant hospital records were reviewed for the all women's. Additional data form was created to extract demographic and clinical data, microbiology (isolated pathogens and antibiograms) and outcome information from inpatient data and ambulatory medical records. Surveillance of patients continued for 30 days after hysterectomy.

MICROBIOLOGICAL METHODS

All samples were obtained from women with clinical symptoms of tubo-ovarian infections. Microbial isolates were identified using standard microbiological techniques, including automated microbiology testing (Vitek-2; bioMe´rieux, Marcy l'Etoile, France). Antibiotic susceptibility testing was performed by using the disk diffusion method (Kirby – Bauer antibiotic testing) according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Strains in the intermediate range were classified as resistant for data analysis.

ETHICS

The Shupyk National Healthcare University of Ukraine Ethics Committee approved this study. In this study all participants signed an informed consent and each had a unique identification number assigned to protect their privacy.

STATISTICAL ANALYSIS

The prevalence of healthcare-associated tubo-ovarian infections in women was presented as a percentage of the total number of women undergoing gynecological surgery. We analyzed samples from women's in the context of a study about microbiology of tubo-ovarian infections and antimicrobial resistance of responsible pathogens. The analysis of statistical data was performed using Excel. Results are expressed as median (range), mean standard deviation for continuous variables, and number and corresponding percentage for qualitative variables. Comparisons were undertaken using Student's t-test and Fisher's exact test for categorical variables. Statistical significance was defined as $P<0.05$.

RESULTS

PREVALENCE OF TUBO-OVARIAN INFECTIONS

In this study during the study period (from 2019 to 2021), 476 of 1,528 patients were found to have healthcare-associated tubo-ovarian infections. The prevalence

Table I. Types of healthcare-associated tubo-ovarian infections among female in Ukraine (P < 0.05)

Type of infections	Cases of tubo-ovarian infections		95% CI
	n	%	
Infection of the Fallopian tubes (Salpingitis)	226	47.5	46.2 – 48.9
Infection of the ovaries (Oophoritis)	162	34.0	32.8 – 35.2
Tubo-ovarian abscess	88	18.5	17.5 – 19.5
Total	476	100.0	

CI, confidence interval.

Table II. Demographic and Social characteristics of patients with healthcare-associated Tubo-ovarian infections in Ukraine (P < 0.05)

Variables	Number of participants (n=1528)	Tubo-ovarian infections (n=476)		95% CI
		n	%	
Age of participants				
16–20	59	24	40.7	39,4 – 41.9
21–25	169	62	36.7	35.5 – 37.9
26–30	209	81	38.8	37.5 – 40.1
31–35	187	69	36.9	35.7 – 38.1
36–40	298	72	24.2	23.1 – 25.3
41–45	244	54	22.1	21.0 – 23.2
46–50	201	58	28.9	27.7 – 30.1
51-55	161	56	34.8	33.6 – 35.9
Marital status				
Single	316	98	31.0	29.8 – 32.2
Married	734	174	23.7	22.6 – 24.9
Divorced	478	204	42.7	41.4 – 43.9
Residence				
Rural	703	194	27.6	26.5 – 28.7
Urban	825	282	34.2	33,0 – 35.4
Educational status				
College and above	723	201	27.8	26.6 – 29.0
Highs school	805	275	34.2	33.0 – 35.4
Occupational status				
Employed	408	111	27.2	26.1 – 28.3
Merchant	387	121	31.3	30.1 – 32.5
Students	300	104	34.7	33.5 – 35.9
Unemployed	433	140	32.3	31.1 – 33.5

HAI, healthcare-associated infection
CI, confidence interval.

of healthcare-associated tubo-ovarian infections in female in Ukraine was 31.2% [95% confidence interval (CI) 30.0-32,4]. Of these cases, 47.5% (226/476) Salpingitis, 34% (162/476) Oophoritis, and 18.5% (88/476) Tubo-ovarian abscess (TOA) were identified (Table I). Of 476 cases tubo-ovarian infections in female, 74.7% were detected after hospital discharge. None of the patients died as a result of these infections. The prevalence of healthcare-associated tubo-ovarian infections in women differed according to the surgical procedure types. The incidence of tubo-ovarian infections was 12.9% after abdominal hysterectomy and 18.3% after vaginal hysterectomy.

A total of 1,528 women in reproductive age (16 – 55 years) participated in the study. The median age of the women was 28 years. The proportion of healthcare associated tubo-ovarian infections was higher in divorced (42.7 %) than marred women (23.7 %). Demographic and Social characteristics of patients with healthcare associated tubo-ovarian infections of the female reproductive tract in Ukraine are presented in Table II.

Table III. Types of microorganisms (n=1428) isolated from 476 patients with healthcare associated Tubo-ovarian infections in Ukraine

Microorganism	All isolates	
	n	%
Gram-positive cocci	359	26,4
Staphylococcus aureus	117	8,2
Enterococcus faecalis	107	7,5
Streptococcus spp.	64	4,5
Staphylococcus epidermidis	63	4,4
Enterococcus faecium	8	0,6
Gram-negative bacilli	1069	74,9
Escherichia coli	396	27,7
Enterobacter spp.	174	12,2
Klebsiella pneumoniae	137	9,6
Pseudomonas aeruginosa	116	8,1
Proteus mirabilis	73	5,1
Acinetibacter spp.	57	4,0
Serratia spp.	55	3,9
Citrobacter spp.	44	3,1
Klebsiella oxytoka	17	1,2

ANTIBIOTIC PROPHYLAXIS

For Ukraine antibiotic prophylaxis at surgery and gynecological procedure is standard practice. In this study of 1,528 women's undergoing a laparoscopic hysterectomy procedure were prescribed Cefazolin (62%) or Cefotaxime (38%). However, 476 (31.2%) of 1,528 patients developed tubo-ovarian infections.

RESPONSIBLE PATHOGENS

In this study, a total of 1,428 pathogens isolated from 476 women with healthcare associated tubo-ovarian infections in Ukraine were analyzed using culture based methods. Of these pathogens, gram-negative bacilli make up 74.9% (1,069/1,428) and 25.1% (359/1,428) gram-positive cocci from of all isolates. The predominant pathogens of healthcare associated tubo-ovarian infections were: *Escherichia coli* (27.7%), *Enterobacter* spp. (12.2%), *Klebsiella pneumoniae* (9.6%), *Staphylococcus aureus* (8.2%), *Pseudomonas aeruginosa* (8.1%), and *Enterococcus faecalis* (7.5%), followed by *Proteus mirabilis* (5.1%), *Streptococcus* spp. (4.5%), *Staphylococcus epidermidis* (4.4%), and *Acinetibacter* spp. (4%). The distribution of microorganisms causing tubo-ovarian infections of the female in Ukraine is shown in Table III.

ANTIMICROBIAL RESISTANCE

Staphylococcal strains (*S.aureus*) displayed a most resistance to penicillin (75.7%) and erythromycin (53.5%). In this study methicillin-resistance was observed in 16.8% of *S. aureus* (MRSA). However, Staphylococcal isolates showed susceptibility to most of the other antimicrobials tested. No strains resistant to linezolid, teicoplanin, vancomycin, tigecycline, and fusidic acid were found.

Streptococcal isolates demonstrated a noteworthy resistance against erythromycin (57.1%) and benzylpenicillin (42.3%), followed by ampicillin (26.5%). Most of the Streptococcal strains were sensitive to clindamycin (94.3%), gentamycin (92.7%), cefuroxime (96.3%), and linezolid (100%).

E. faecalis isolates were not sensitive to cefuroxime, clindamycin, and trimethoprim-sulfamethoxazole. Approximately, 23.6% of the *E. faecalis* isolates displayed resistance to aminoglycosides and 14.9% was resistant to quinolones. No strains resistant to vancomycin.

The overall proportion of extended spectrum betalactamases (ESBL) production among Enterobacteriaceae was 24.7%. The prevalence of ESBL production among *E. coli* isolates was 28.6%. *E. coli* was most sensitive (>90%) to ertapenem, cefotaxime, ceftazidime, imipenem, piperacillin/tazobactam and high (>60%) resistance to cefuroxime, amoxicillin, and levofloxacin. *E.coli* strains were high (>50%) resistance to cefazolin. Antimicrobial resistance to third-generation cephalosporins was observed in 14.9% *E.coli* isolates.

Isolates of *Enterobacter* spp. was most sensitive (>90%) to ciprofloxacin, cefotaxime, piperacillin/tazobactam, ceftazidime and ticarcillin. No strains of *Enterobacter* spp. resistant to cefepime, meropenem, imipenem, and ertapenem were found. *Enterobacter* spp. strains were high (>50%) resistance to ampicillin/sulbactam, ampicillin, cefazolin, amoxicillin/clavulanic acid, clindamycin, ciprofloxacin, and high percentage resistance to gentamycin (43.4%), cefaperazon (39.1%) and ceftriaxon (29.8%).

K. pneumoniae isolates showed high susceptibility to piperacillin/tazobactam, ertapenem, meropenem, imipenem, levofloxacin, and gentamycin. However, these stranis while

ones exhibited a noticeable percentage (>35%) of resistance to ampicillin, amoxicillin/clavulanic acid, ofloxacin, and ciprofloxacin. The prevalence of ESBL production among *K. pneumoniae* isolates was 12.8%. Resistance of *K. pneumoniae* strains to third generation cephalosporins was observed in 11.3%.

P. aeruginosa isolates demonstrated remarkable resistance (>35%) to cefepime, gentamycin, and cefoperazone, and resistance (>45%) to cefazolin. This isolates was most sensitive to meropenem (>80%), imipenem (>80%), piperacillin/tazobactam (>90%), and ceftazidime (>85%). Carbapenem resistance was identified in 11.3% of *P.aeruginosa* isolates.

DISCUSSION

This study presents the estimates of the current prevalence of healthcare associated tubo-ovarian infections of the female and antimicrobial resistance of responsible pathogens in Ukraine. The prevalence of healthcare-associated tubo-ovarian infections was 31.2%. Of these cases, Salpingitis, Oophoritis, and tubo-ovarian abscess (TOA) were 47.5%, 34% and 18.5%, respectively. Of all cases tubo-ovarian infections in female, 74.7% were detected after hospital discharge. Available literatures there are no epidemiologic studies (prevalence or incidence) of different types of healthcare-associated tubo-ovarian infections of the female. Therefore, we were unable to compare our results with other studies in other countries.

TOA are known to be rare complications from pelvic inflammatory disease. Often the theoretical basis for bacterial seeding of the Fallopian tube and ovary is an ascending infection through the uterus. Pelvic inflammatory disease after hysterectomy is rare and the underlying route of infection is highly heterogeneous. A review of the case reports published on this subject showed that pelvic inflammatory disease shoved not be excluded in patients with a history of hysterectomy when symptoms and findings are compatible. [10]. In this study presents cases of a TOA in women after a hysterectomy. Although it is known that TOA can occur in the presence of adjacent appendicitis or diverticulitis. However, these patients did not have either. Therefore, the mechanism for infection in these patients in our study was a subacute condition preceding her hysterectomy. The average time between the hysterectomy and the onset of the symptoms of TOA are highly heterogeneous. Some authors have reported cases of TOA from 8 months up to 12 years after the surgery [11-13]. Tubo-ovarian abscess develops in both women who have undergone both an abdominal hysterectomy [13, 14] and a vaginal hysterectomy [12]. The prevalence of healthcare-associated tubo-ovarian infections in women differed according to the surgical procedure types. In our study the incidence of tubo-ovarian infections was 12.9% after abdominal hysterectomy and 18.3% after vaginal hysterectomy.

In this study, the predominant pathogens of tubo-ovarian infections were: *E. coli, Enterobacter* spp., *K. pneumoniae, S. aureus*, *P. aeruginosa*, and *E. faecalis*, followed by *P. mirabilis*, *Streptococcus* spp., *S. epidermidis*, and *Acinetibacter* spp. Our results was coherent with reports other studies [5, 15, 16]. In addition, *Gardella vaginalis*, *Enterococcus* sp., *Streptococcus* spp., *E. coli,* and *Candida Albicans* have been reported in TOAs [17-19]. Pathogens of tubo-ovarian infections are often not isolated in cultures.

In literature is scant information is available on the antimicrobial susceptibility of responsible pathogens of tubo-ovarian infections. Therefore, this was the basis for this study. In present study, methicillin-resistance was observed in 16.8% of *S. aureus* (MRSA). No strains *S.aureus* and *E.faecalis* resistant to vancomycin. The overall proportion of extended spectrum beta-lactamases (ESBL) production among Enterobacteriaceae was 24.7%. The prevalence of ESBL production among *E. coli* isolates was 28.6% and among *K. pneumoniae* 12.8%. Resistance to third-generation cephalosporins was observed in 14.9% *E.coli* and 11.3% *K. pneumoniae* isolates. Carbapenem resistance was identified in 11.3% of *P.aeruginosa* isolates. Available literatures there are no studies on antimicrobial resistance responsible pathogens of healthcare-associated tubo-ovarian infections of the female. Therefore, we were unable to compare our results with other studies in other countries.

According to literature, current international guidelines for the management of pelvic inflammatory disease recommend the prescription of antibiotics for prophylactic and treatment [20-22]. The appointment of an inadequate starting therapy decreases the effectiveness of treatment [23, 24]. In our study, 31.2% of patients who were prescribed antibiotics developed tubo-ovarian infections. Possibly, this is due to the high levels of antimicrobial resistance of causing pathogens of healthcare associated tubo-ovarian infections of the female in Ukraine. There is therefore need the treatment and prevention of tubo-ovarian infections of the female with Gram negative bacteria needs to be changed in Ukraine. However, the data are limited and more studies are needed to guide a change in first-line antibiotic treatment or prophylactics. If the infection becomes severe and a TOA occurs, only about 70% of the infections are resolved with conservative treatment, and surgery is often necessary. Laparoscopic drainage of abscesses should be considered in such TOA patients. Laparoscopic surgery is less invasive than laparotomies, and features less blood loss, shorter hospitalization, less postoperative fever, and fewer intraoperative complications. However, in patients with intestinal tract adhesions or generalized peritonitis, switching to a laparotomy is recommended. Surgery for fallopian tube abscesses need to preserve normal ovary tissue to avoid the postoperative loss in the ovarian reservation. Precautions include removal of the source of infection to avoid a subsequent need for a hysterectomy.

STRENGTHS AND LIMITATIONS

The absence of national surveillance data on reproductive tract infections in Ukraine compelled us to rely entirely on data from the only study prevalence of health-

care associated tubo-ovarian infections of the female. The strengths of the present study lie in the application of CDC/NHSN methodology for surveillance. Indicators of healthcare associated tubo-ovarian infections provided by surveillance activities require comparison with adequate reference data to stimulate further infection control actions and to enhance quality of health care. The limitations of this study include in conduct at a in hospitals from only seven regions of Ukraine. Therefore, the results present study not is representative of other hospitals of Ukraine.

CONCLUSIONS

Healthcare associated tubo-ovarian infections of the female in Ukraine are a common occurrence and many cases are caused by pathogens that are resistant to antibiotics. Microbiological monitoring of the prevalence of etiologic agents of healthcare associated tubo-ovarian infections of the female and antimicrobial resistance is necessary to enhance our knowledge of its epidemiology and treatment. Treatments need to be adjusted on a case-by-case basis depending on the severity of the patient's condition and antimicrobial resistance of the responsible pathogens. Results this study suggest that the prevention and treatment of tubo-ovarian infections of the female in Ukraine needs to be changed. However, the data are limited and more studies are needed. The present study provides valuable data as a first study for national surveillance of healthcare associated tubo-ovarian infections of the female and potential for comparison with data from other countries.

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The Authors declare no conflict of interest

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