ORIGINAL ARTICLE

CONTENTS

Endometritis after hysteroscopic procedures in Ukraine: results a multicenter study

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ABSTRACT

Aim: To determine the current prevalence of endometritis after hysteroscopic procedures and antimicrobial resistance of responsible pathogens in Ukraine.

Materials and Methods: Multicenter prospective cohort study was conducted from January 2020 to December 2022 in fifteen hospitals from twelve regions of Ukraine. Definitions of endometritis were adapted from the Centers for Disease Control and Prevention's National Healthcare Safety Network. Antibiotic susceptibility was done by the disc diffusion test as recommended by EUCAST.

Results: Among 13,872 patients with hysteroscopic procedures, 1027 (7.4%) endometritis were observed. Of these cases, 0.4% were detected after diagnostic hysteroscopy, and 7.0% were detected after operative hysteroscopy. Of all endometritis cases, 64.2% were detected after hospital discharge. The most commonly reported bacterial species were *Escherichia coli* (24.3%), followed by *Enterobacter* spp. (12.7%), *Enterococcus* spp. (8.3%), *Pseudomonas aeruginosa* (8.1%), *Serratia marcescens* (6.8%), *Staphylococcus aureus* (5.9%), *Proteus mirabilis* (5.8%), *Klebsiella oxytoca* (5.1%), *Stenotrophomonas maltophilia* (4.5%), *Klebsiella pneumoniae* (4.1%). A significant proportion of patients were affected by endometritis caused by bacteria developed resistance to several antimicrobials, varying widely depending on the bacterial species, antimicrobial group, and geographical region of Ukraine.

Conclusions: Our data suggest a high prevalence of endometritis after hysteroscopic procedures. Risk for endometritis was higher after operative hysteroscopy compared with diagnostic hysteroscopy. Many most of patients were affected by endometritis caused by bacteria developed resistance to several antimicrobials. These data underscore the importance of tracking antimicrobial resistance of responsible pathogens of HAIs in hospitals.

KEY WORDS: hysteroscopic procedure, endometritis, responsible pathogens, antibiotic prophylaxis, antimicrobial resistance, Ukraine

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INTRODUCTION

Maternal morbidity are global socioeconomic and healthcare burdens, and healthcare-associated infections account for a significant, and often preventable, portion of that burden. Endometritis, primarily caused by bacterial pathogens, leading to poor reproductive performance [1]. Inflammation of the uterus can cause scarring, which prevents an embryo from implanting and developing normally within the uterine wall [2, 3]. In a prospective study, Kamiyama et al. [4] have demonstrated a negative biological effect of bacterial endotoxin in vitro fertilization – embryo transfer (IVF-ET) treatment, suggesting a link between endotoxin levels in menstrual effluent and pregnancy rate. Endotoxins are part of the outer membrane of the cell wall of Gram-negative pathogens such as *Escherichia coli*, *Salmonella, Shigella, Pseudomonas, Neisseria, Haemophilus influenza* [5]. Repeated implantation failure (RIF) and recurrent pregnancy loss (RPL) impose a heavy burden on women desiring children, especially when etiology is unclear [6]. Implantation failure has been identified by the European Society of Human Reproduction and Embryology as one of the main unresolved issues in reproductive medicine.

Endometritis is a condition involving the breakdown of the peaceful co-existence between microorganisms and the host immune system in the endometrium. Conventionally, the uterine cavity is assumed to be sterile, but in fact, microorganisms have been detected in the endometrial cavity of non-pregnant women. It has been

proposed that microorganisms ascending from the lower genital tract could colonize the uterine cavity; however, host mechanisms have been expected to restrict bacterial proliferation and invasion. These mechanisms involve the cervical mucus plug [7], the endometrial epithelium and its immune cellular components (neutrophils, macrophages, and natural killer cells), and elements of the innate immune system, including natural antimicrobial peptides present in the endometrium [8].

Infections that occur after hysteroscopic surgery can result in considerable ill health for the women. The prescription of antibiotics after an hysteroscopic surgery has become routine practice to overcome this situation in Ukraine. Faced with increasing antimicrobial resistance because of misuse and over-prescription of antibiotics, we need evidence about the effect of routine intake of antibiotics for preventing infections after hysteroscopic surgery. Currently, prevalence of endometritis after hysteroscopic surgery in women and the bacteria responsible for these infections have not been adequately studied.

AIM

The aim this study to determine the current prevalence of endometritis after hysteroscopic procedures in women and antimicrobial resistance and antimicrobial resistance of responsible pathogens in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTING AND POPULATION

We performed a multicentre prospective cohort study was based on surveillance data for healthcare-associated infections (HAIs). The study population consisted of all women who had a hysteroscopic procedures from January, 2020, to December, 2022, and who received postoperative care in gynecological departments at fifteen general hospitals from twelve regions of Ukraine. All hospitals which are similar in terms of medical equipment, personnel, and laboratory facilities. Indications for the operative hysteroscopies included abnormal uterine bleeding, ultrasound or hysterographic findings indicative of intrauterine lesions, dysfunctional uterine bleeding. Exclusive criteria were pregnancy, cervical carcinoma, pelvic inflammatory disease and excessive bleeding. Hysteroscopies were performed in the above departments. First a diagnostic hysteroscopy was performed and afterwards the final diagnostic operative hysteroscopy was performed at the same time in the majority of the study population. The diagnostic hysteroscopies were performed using a standard 4-mm hysteroscope. Using a resectoscope submucous myomas and endometrial polyps were resected or a transcervical resection of endometrium (TCRE) was performed. In total TCRE the entire uterine cavity was treated together with the upper part of the endocervix.

DEFINITION

The criteria for endometritis after hysteroscopic surgery were adapted from the Centers for Disease Control and Prevention's (CDC) and National Healthcare Safety Network's (NHSN) case definitions. Endometritis must meet at least one of the following criteria: (a) patient has organism(s) identified from endometrial fluid or tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment, for example, not Active Surveillance Culture/Testing (ASC/AST), (b) patient has suspected endometritis with at least two of the following signs or symptoms: fever (>38.0°C), pain or tenderness (uterine or abdominal) with no other recognized cause, or purulent drainage from uterus. Any bacterial isolate of the species under surveillance found in a sample taken from a normally sterile body fluid may be considered a pathogen.

DATA COLLECTION

Hospital staff participating in HAI surveillance underwent a training course that covered endometritis case definitions and diagnoses, and instructions for surveillance data collection and reporting. We developed a special questionnaire that collected data from medical records, including, age (years), discharges of patients, microbiological and radiographic investigations, hysteroscopic procedures, antibiotics usage, and culture and sensitivity of the clinical isolates. Follow-up of each patient was continued for one month after hysteroscopic procedures. The discharged patients were advised for ongoing follow-up care for a month after hysteroscopic procedures in the outpatient department. Information regarding the postoperative period following discharge was obtained from the outpatient records and from records documenting follow-up by referring gynecologists.

MICROBIOLOGICAL METHODS

In this study, pathogen strains were identified by an automated microbial identification system. The interpretation of antimicrobial susceptibility testing results was evaluated for strains with a correct species identification. The evaluation was performed according to the clinical breakpoints in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical Breakpoints Tables v12.01, with the EUCAST categories

Table 1. Distribution of 1,027 endometritis cases in women after hysteroscopic procedures in Ukrainian hospitals, 2020-2022

Type of procedure	Number of patients	Endometritis		95% CI
		n	%	
Diagnostic hysteroscopy	8248	49	0.6	0.5 - 0.7
Operative hysteroscopy	5624	978	17.4	17.1 - 17.7
Total	13,872	1,027	7.4	7.2 - 7.6

Table 2. Distribution of pathogens isolated from patients with endometritis after hysteroscopic procedures in Ukraine, 2020-2022

Microorganisms	Number of isolates (n)	Percentage (%)
Gram-positive cocci	292	21.0
Enterococcus spp.	115	8.3
Streptococcus pneumoniae	41	2.9
Coagulase-negative staphylococci	54	3.9
Staphylococcus aureus	82	5.9
Gram-negative bacilli	1106	79.5
Escherichia coli	338	24.3
Klebsiella pneumoniae	57	4.1
Klebsiella oxytoca	71	5.1
Enterobacter spp.	177	12.7
Proteus mirabilis	81	5.8
Serratia marcescens	95	6.8
Stenotrophomonas maltophilia	62	4.5
Citrobacter spp.	52	3.7
Pseudomonas aeruginosa	113	8.1
Acinetobacter baumannii	45	3.2
Fungi	9	0.6
Candida albicans	9	0.6
Total	1392	100.0

"susceptible, standard dosing regimen" (S), "susceptible, increased exposure" (I), and "resistant" (R). An isolate is considered resistant to an antimicrobial agent when tested and interpreted as R in accordance with the clinical breakpoint criteria used by the local laboratory. Meticillin-resistant *Staphylococcus aureus* (MRSA) is based on AST results for cefoxitin or, if unavailable, oxacillin. AST results reported for cloxacillin, dicloxacillin, flucloxacillin or meticillin are accepted as a marker for oxacillin resistance if oxacillin is not reported.

ETHICS

All patients gave written consent before the procedure and the study was approved by the Institutional Research Ethics Committee of Shupyk National Healthcare University of Ukraine. All data from patients were anonymized prior to analysis.

STATISTICAL ANALYSIS

All clinical and microbiological data were entered in an Excel (Microsoft Corp., Redmond, WA, USA) database for statistical analysis. Results this study are expressed as median (range), mean ± standard deviation for continuous variables, and number and corresponding percentage for qualitative variables. Proportions of total endometritis cases meeting specific CDC/NHSN criteria were calculated, and characteristics of each category were compared by using Fisher's exact test. All statistical analyses were two-sided and significance was set at $P < 0.05$.

RESULTS

PREVALENCE OF ENDOMETRITIS

Of the 13,872 patients evaluated, 8,248 underwent a diagnostic hysteroscopy and 5,624 underwent an opera-

tive hysteroscopy. During the study period, 1027 (7.4%) of 13,872 patients after hysteroscopic procedures were found to have endometritis. Of the total endometritis cases, 64.2% were detected after hospital discharge. The prevalence of endometritis after hysteroscopic procedures

in Ukrainian hospitals was 7.4% (95% confidence interval [CI] 7.2-7.6), and the prevalence of endometritis in different types procedures was: after diagnostic hysteroscopy, 0.4% (95% CI 0.3-0.5), and after operative hysteroscopy, 7.0% (95% CI 6.9-7.3). The distribution of endometritis after hysteroscopic procedures in Ukrainian hospitals is shown in Table 1. The risk for endometritis was similar for endometrectomy, fibroma, or polyp resections.

RESPONSIBLE PATHOGENS

A total number of reported isolates from patients with endometritis after hysteroscopic procedures in 2020-2022 were 1392. The most commonly reported bacterial species in 2020-2022 were *Escherichia coli* (24.3%), followed by *Enterobacter* spp. (12.7%), *Enterococcus* spp. (8.3%), *Pseudomonas aeruginosa* (8.1%), *Serratia marcescens* (6.8%), *Staphylococcus aureus* (5.9%), *Proteus mirabilis* (5.8%), *Klebsiella oxytoca* (5.1%), *Stenotrophomonas maltophilia* (4.5%), *Klebsiella pneumoniae* (4.1%), Coagulase-negative staphylococci (3.9%), *Citrobacter* spp. (3.8%), *Acinetobacter baumannii* (3.2%), *Streptococcus pneumoniae* (2.9%). Distribution of pathogens isolated from patients with endometritis after hysteroscopic procedures are presented in Table 2.

ANTIMICROBIAL RESISTANCE

During study period the antimicrobial resistance (AMR) situation reported by Ukrainian hospitals varied widely, depending on the bacterial species, antimicrobial group and geographical region, as demonstrated by both varying AMR percentages and estimated incidences of endometritis with resistant bacteria. The reported AMR percentages and estimated incidences of endometritis with resistant bacteria varied widely among Ukrainian regions, often with a north-to-south and west-to-east gradient. In general, the lowest AMR percentages were reported by hospitals in the north of Ukraine and the highest by countries in the south and east of Ukraine.

In hospitals, more than half of the *E. coli* isolates reported, and almost a third of the *K. pneumoniae* isolates, were resistant to at least one antimicrobial group, and combined resistance to several antimicrobial groups was a frequent occurrence. With one notable exception (i.e. carbapenem resistance in *K. pneumoniae*), both *E. coli* and K. pneumoniae saw either decreasing trends in the Ukraine, or no trend. For third-generation cephalosporin-resistant *E. coli*, a decreasing trend in the estimated incidence of endometritis was also noted from 2020 to 2022 for the Ukraine with a 16.8% decrease in 2022 against the baseline year 2020. Among antimicrobial groups monitored for both species, mean AMR percentages were generally higher in *K. pneumoniae* than in *E. coli*.

Carbapenem resistance remained rare in *E. coli*, but almost one third of Ukrainian hospitals reported carbapenem resistance percentages above ≥10% in *K. pneumoniae*. There was a significantly increasing trend in the estimated incidence of endometritis with carbapenem-resistant *K. pneumoniae*, with a 19.5% increase in 2022 against the baseline year 2020. Carbapenem resistance was also common in *P. aeruginosa* and *A. baumannii*, with a higher mean percentage than in *K. pneumoniae*. For most gram-negative bacteria, increases in the Ukrainian hospitals mean AMR percentages between 2020 and 2022 were moderate, although AMR remained at high levels.

For *S. aureus*, a significantly decreasing trend in the hospitals mean percentage of meticillin-resistant *S. aureus* (MRSA) isolates (8.1%), and in the estimated incidence of endometritis with MRSA was reported during the period 2020–2022. In addition to the increase in the number of reported isolates in 2022 compared to 2020, the last five years have seen a significantly increasing trend for mean percentage of macrolide resistance and penicillin non-wild-type, including combined resistance in *S. pneumoniae*. One development of particular concern was that the significantly increasing trend in the mean percentage of vancomycin-resistant isolates of *Enterococcus* spp. rose further, from 10.2% in 2020 to 14.7% in 2022.

DISCUSSION

In the present study, to the best of our knowledge the largest prospective, controlled study to date, we evaluated the prevalence of endometritis after both diagnostic and operative hysteroscopy, and antimicrobial resistance of responsible pathogens. Our data suggest a high prevalence of endometritis after hysteroscopic procedures. Risk for endometritis was higher after operative hysteroscopy compared with diagnostic hysteroscopy. The present study found that a significant proportion of study population were affected by endometritis caused by bacteria developed resistance to several antimicrobials.

Hysteroscopy is a minimally invasive gynecological procedure and is considered the gold standard for the

treatment of intracavitary benign uterine pathology. This minimally invasive technique can be associated with serious complications that can lead to severe morbidity. As for any surgical intervention, there is a risk of infection after surgery. However, the rate and severity of such complications is poorly documented. Few authors have specifically evaluated the infectious risk according to the operative procedure. The epidemiology of HAIs after hysteroscopic procedures has not been well characterized. In part this is because of the limitations of surveillance systems, which usually monitor infections after hysteroscopic procedures that are recognized during hospitalization.

According to the literature, prevalence of endometritis after hysteroscopic procedures is estimated is between 0.01% [9] and 2.1% [10]. In our study, the prevalence of endometritis after hysteroscopic procedures in Ukrainian hospitals was 7.4% (95% CI 7.2-7.6%), and the prevalence of endometritis in different types procedures was: after diagnostic hysteroscopy, 0.4% (95% CI 0.3-0.5%), and after operative hysteroscopy, 7.1% (95% CI 6.9-7.3%). Of all endometritis cases, 64.2% were detected after hospital discharge. The risk for endometritis was similar for endometrectomy, fibroma, or polyp resections.

In this study a total, 1392 strains (Gram-negative and -positive bacteria, and fungi) were isolated from 1027 patients with endometritis after hysteroscopic procedures. The predominant endometritis pathogens were: *E. coli*, *Enterobacter* spp., *Enterococcus* spp., *P. aeruginosa*, *S. marcescens*, *S. aureus, P. mirabilis, Klebsiella oxytoca, S. maltophilia,* and *K. pneumoniae*. The antimicrobial resistance (AMR) situation reported by Ukrainian hospitals for 2020-2022 varied widely, depending on the bacterial species, antimicrobial group and geographical region, as demonstrated by both varying AMR percentages and estimated incidences of endometritis with resistant bacteria.

Previous studies found a high prevalence of HAI caused by multidrug-resistant organisms (MDROs), varying on geographical region of Ukraine. The majority of MDRO isolates carried b-lactamase genes [11-14]. These data underscore the importance of tracking antimicrobial resistance in hospitals.

Endometritis occurs as a result of an infection in the lining of the uterus, known as the endometrium. Such infections may develop due to abnormal bacteria, or bacteria usually found in the vagina. The cervix is the opening to the uterus, and it usually keeps bacteria out of the uterus. However, bacteria can get in when the cervix is open. This may happen for various reasons, such as during childbirth or surgery. Possible risk factors for endometritis include childbirth or pregnancy loss, cesarean delivery, sexually transmitted infections, bacteria in the uterus, pelvic inflammatory disease, and pelvic procedures [12, 13].

Recognizing these risk factors is crucial in identifying and addressing endometritis, as they can contribute to the development of this condition and guide preventive measures and treatment strategies. According to the literature, antibiotic treatment in case of endometritis in women with repeated implantation failure or recurrent pregnancy loss may increase the chances for live birth [1,6].

According to the literature clinical hysteroscopic procedures were mainly applied for diagnosis and therapy (such as diagnostic hysteroscopy, operative hysteroscopy and hystero resectoscopy). They may involve different operative processes, such as visually diagnostic checking, or with retrograde operations [15]. Thus far, infection after hysteroscopy is uncommon, but its prevalence is estimated at approximately around 1% of cases [16]. Thus antibiotic prophylaxis is not commonly considered to be a standard therapy, and its effects have not been specifically identified. However, postoperative infection complications are still a major concern in perioperative period because hysteroscopic procedures were performed in the relatively contaminated area, which has abundant bacterial flora, and the transcervical route may increase, per se, such a potential risk of local dysbacteriosis [17, 18]. In addition, hysteroscope insertion and removal may transfer vaginal and cervical flora into the uterine cavity. More importantly, a randomized controlled trial firstly reported by Bhattacharya claimed applying prophylactic antibiotics could significantly decrease the incidence of bacteremia for patients who underwent hysteroscopic surgery but revealed no clinical benefit for reducing essential infection rate [19]. Thus, so far, the clinical value of antibiotic prophylaxis for hysteroscopy is not well defined, and there is no relevant guideline for prophylactic antibiotic standardization. Currently, there are no randomised controlled trials that assess the effects of prophylactic antibiotics on infectious complications following transcervical intrauterine procedures. It is, therefore, not possible to draw any conclusions regarding the use of prophylactic antibiotics for the prevention of post-procedure transcervical intrauterine infections [20].

Meanwhile, the indiscriminate use of antibiotics has been associated with the development of antibiotic-resistant bacteria, and additional antibiotics may cost unnecessary medical expenses. Considering these drawbacks, we conclude that antibiotic prophylaxis is not recommended during hysteroscopic procedures as long as standardized aseptic procedures are performed.

However, faced with increasing antimicrobial resistance because of misuse and over-prescription of antibiotics, we need evidence about the effect of routine intake of antibiotics for preventing infections after hysteroscopic procedures. Given these findings, we concluded that antibiotic prophylaxis brought no clinical benefit for patients who underwent hysteroscopic procedures.

STRENGTHS AND LIMITATIONS

One strength of this study was that it was a prospective multi-centre observational cohort study, based on endometritis after hysteroscopic procedures surveillance data and using CDC/NHSN methodology. In the present study, to the best of our knowledge the largest prospective, controlled study to date, we evaluated the prevalence of endometritis after both diagnostic and operative hysteroscopy, and antimicrobial resistance of responsible pathogens. Also, this was the first study of phenotypic characterization of antibiotic resistance of responsible pathogens isolated from patients with endometritis after hysteroscopic procedures. Limitations of the study included that it was performed in fifteen hospitals only, and the prevalence of endometritis after hysteroscopic procedures and antimicrobial resistance and antimicrobial resistance of responsible pathogens in other hospitals was not investigated.

CONCLUSIONS

Our data suggest a high prevalence of endometritis after hysteroscopic procedures. The most of endometritis result from iatrogenic trauma to the uterine wall that occur during operative hysteroscopy, which allows for the introduction of bacteria into these normally sterile environments. Risk for endometritis was higher after operative hysteroscopy compared with diagnostic hysteroscopy. A significant proportion of patients were affected by endometritis caused by bacteria developed resistance to several antimicrobials, varying widely depending on the bacterial species, antimicrobial group, and geographical region of Ukraine. These data underscore the importance of tracking antimicrobial resistance of responsible pathogens of HAIs in hospitals. To reduce antimicrobial resistance of aetiologic agents of endometritis after hysteroscopic procedures, it is necessary to develop and implement advanced infection control measures based on HAI surveillance data. Lack of evidence on the effect of routine antibiotic prescription for prevention infections after hysteroscopic procedures and antimicrobial resistance calls for further research. Optimizing the antibiotic prophylaxis may reduce the burden of infection after hysteroscopic procedures, but prevention is the key element.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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