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ORIGINAL ARTICLE

URINARY TRACT INFECTIONS IN PREGNANT WOMEN IN UKRAINE: RESULTS OF A MULTICENTER STUDY (2020-2022)

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ABSTRACT

The aim: To obtain the first national estimates of the current prevalence rate of urinary tract infections (UTIs) in pregnant women and antimicrobial resistance of causing pathogens in Ukraine.

Materials and methods: Prospective multicentre cohort study was conducted from January 2020 to December 2022. The study population consisted of 36,876 pregnant women from 17 regions of Ukraine. Antibiotic susceptibility was done by the disc diffusion test as recommended by European Committee on Antimicrobial Susceptibility Testing guidelines.

Results: A total 29.5% pregnant women were found to have UTIs. Among these cases, 36.5% Asymptomatic bacteriuria, 51.7% Cystitis and 11.8% Pyelonephritis were observed. Of all cases, 87.9% were defined as healthcare-acquired UTIs and 12.1% community-acquired UTIs. The most common uropathogen was Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. Many uropathogens isolated from UTI cases were found to be multidrug resistant.

Conclusions: UTIs in pregnant women in Ukraine is a common occurrence and many cases are caused by pathogens that are resistant to antibiotics. Optimizing the management and empirical antimicrobial therapy may reduce the burden of UTIs in pregnant women, but prevention is the key element.

KEY WORDS: pregnant women, healthcare-associated urinary tract infection, community-acquired urinary tract infection, asymptomatic bacteriuria, pyelonephritis, antimicrobial resistance, Ukraine

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INTRODUCTION

Urinary Tract Infections (UTIs) are one of the most common microbial diseases among the pregnant women threat worldwide [1]. UTIs are the most common type of infection during pregnancy, affecting from 10% [2, 3] to 24.3% [1] of pregnant women. The spectrum of UTIs in pregnant women ranges from lower urinary tract disease (asymptomatic bacteriuria, acute cystitis) to upper urinary tract disease (acute pyelonephritis). According to literature, in pregnant women the incidence of Asymptomatic Bacteriuria (ASB) in pregnant women were from 2-13% to 57.5% and acute cystitis from 1-4% to 35% [1, 4]. It is reported that acute pyelonephritis may also occur in 1-4% of pregnant women [5]. In Ukraine, the prevalence of pyelonephritis in pregnant women is 7.6% [1].

According to literature, UTIs in pregnant women can lead to complications in maternal and fetal complications such as preterm labor, low birth weight, or maternal systemic infection. It is estimated that every tenth pregnant women with pyelonephritis will eventually go into preterm labor [6]. Untreated UTIs in pregnant women may increase the risk of fetal developmental alterations and mental retardation [7]. In addition, UTIs is closely associated with a higher risk of premature rupture of the membranes, premature birth and early neonatal systemic infection [4, 8]. Therefore, such infections pose considerable diagnostic and therapeutic challenges for pregnant women.

Clinical and therapeutic decisions are influenced by numerous factors, including antimicrobial resistance of the causative agents of UTIs. Current guidelines for management of UTIs in pregant women recommend the use of antibiotics for treatment infections. However, the growing antimicrobial resistance is limiting their use for treatment of UTIs in pregnant women in Ukraine. There is currently sparse data characterizing antibiotic resistance of common antepartum infections, such as UTIs, and subsequent clinical ramifications. To date, there is limited data describing the incidence and impact of antibiotic-resistance in obstetric infections other than group B streptococcus [9, 10]. However, the potential implications of antibiotic-resistant urinary tract infections are significant [1, 11]. The consequences of antibiotic-resistant infections in non-pregnant patients are better documented than those in pregnancy. For example, antibiotic-resistant blood stream infections lead to both excess mortality and prolonged hospital stays outside of pregnancy [12]. Similar to other infections outside of pregnancy, urinary tract infections in pregnancy are subject to significant antibiotic resistance. Antibiotic stewardship, as well as knowledge of local resistance patterns and appropriate treatment in pregnancy, are critical for improving outcomes and preventing development of worsening resistance patterns. However, prevalence of UTIs in pregnant women and antimicrobial resistance of causing pathogens in Ukraine are scant. The previous reports of UTIs in Ukraine have been limited only to Healthcare-Associated Infections (HAIs) [13, 14].

THE AIM

The aim of this study was to obtain the first national estimates of the current prevalence rate of UTIs in pregnant women and antimicrobial resistance of causing pathogens in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTINGS AND PARTICIPANTS

We performed a prospective multicenter cohort study was based on surveillance data for UTIs in pregnant women done in 18 women hospitals from 17 Ukrainian regions over 36 months period from January, 2020 to December, 2022. All participants in our study were local residents. The selection criterion for the inclusion in the study was above 18 years. No past history related to any sexually transmitted diseases and immunocompromised status was noted.

DEFINITION

The definition of UTI is an infection in any part of the urinary system, including kidney, ureter, bladder, or urethrae. Urinary tract infection is the presence of the microorganism in the urine. Infections pregnant women were defined as community-acquired urinary tract infection (CA UTI) and healthcare-acquired urinary tract infection (HA UTI). Definitions of healthcare associated urinary tract infection (HA UTI) in pregnant women were used from the CDC/ NHSN guidelines published in 2019. UTIs are classified either as Asymptomatic Bacteriuria (ASB), when the infection is limited to bacterial growth in urine, or symptomatic infections (acute cystitis, acute pyelonephritis), when bacteria invade urinary tract tissues, inducing an inflammatory response. All cases of UTIs was evidenced by urine culture and sensitivity done in urine sample. Two consecutive voided urine specimens (preferably within 2 wk) with the same bacterial species isolated in quantitative count of $>10^5$ CFU/ml in pregnant women were considered to be positive for UTI.

MICROBIOLOGICAL METHODS

We analyzed urine samples from pregnant women's in the context of a study about microbiology of UTIs and antimicrobial resistance of responsible pathogens. Microbial isolates were identified using standard microbiological techniques. Urine samples were obtained from pregnant women with clinical symptoms of UTIs. Urine of all patients was sampled and subjected to routine and microscopy examination and culture. Urine samples were processed by a semi-quantitative dilution method. The significant bacteriuria was 10^5 cfu/ml was taken into consideration while confirmation as UTI. Detected pathogens in significant amounts were identified according to phenotypical characteristics. Antimicrobial susceptibility testing was performed according to EUCAST guidelines at the local laboratories. Isolates with intermediate susceptibility were considered resistant.

DATA COLLECTION

A standard data collection form was created to extract demographic and clinical data, microbiology (isolated pathogens and their antibiograms) and outcome information from routine patient records. Full text relevant hospital records were reviewed for the all pregnant women's. The pregnant women were compared in terms of irritative urinary symptoms, bacteriuria, hematuria, length of hospital stay, and mobilization time. All data were collected using the sign of UTI in this form. In addition, hospital records were scrutinized for the signs and symptoms as per CDC/NHSN criteria for confirmation as HA UTI. Only inpatient samples were considered for analysis. Duplicates were excluded, allowing only one isolate of a given pathogen per patient. Prevalence of major uropathogenic organisms and their antimicrobial susceptibility patterns were analysed.

ETHICS

Institutional Ethical Committee (IEC) of the Shupyk National Healthcare University of Ukraine (Kyiv, Ukraine) clearance was obtained before beginning of the study. Pregnant women's in the hospital, who accepted to be a part of the study, were approached, IEC clearance certificate was shown to the patients and their consent was obtained. All pregnant women's data were anonymised prior to the analysis.

STATISTICAL ANALYSIS

After all the data was collected, a descriptive analysis was conducted to determine the characteristics of the research subjects. The prevalence of UTIs was reported as the percentage of the total number of pregnant women's. Cases of UTIs were analysed by type of infection (asymptomatic bacteriuria, cystitis and pyelonephritis), which were mutually exclusive. The analysis of statistical data was performed using Excel and SPSS 10.0 statistical software package. 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. In our study statistical significance was defined as $P<0.05$.

RESULTS

PREVALENCE OF UTIS

During the study period, 10,879 of 36,876 pregnant women were found to have UTIs. The prevalence of UTIs in Ukraine was 29.5% [95% confidence interval (CI) 29.3-29.7%, $P<0.0001$]. The most frequently reported UTI types were: 36.5% (3,970/10,879) asymptomatic bacteriuria, 51,7% (5,625/10,879) cystitis, and 11.8% (1,284/10,879) pyelonephritis. Among these cases, 87.9% (9,563/10,879) were defined as healthcare-acquired urinary tract infection (HA UTI) and 12.1% (1,316/10,879) community-acquired urinary tract infection (CA UTI). The UTIs cases among pregnant women in the participating hospitals varied significantly. In terms of Ukrainian regions, fluctuations of the indicator values were observed of HA UTI in pregnant women – from the smallest in the west and north while higher percentages were reported in the south, east and central region of Ukraine.

CAUSATIVE AGENTS OF UTIS.

In total, 15,281 specimens were isolated from 10,879 pregnant women with UTIs. Of all UTIs 73.1% (7,956/10,879) were reported to be polymicrobial. Overall, Gram-negative bacteria predominated. Considering all UTI types together, *Escherichia coli* (*E coli*) were most commonly reported, accounting for 54.2% of all organisms, followed by *Klebsiella pneumoniae* (14.2% of all organisms), *Proteus mirabilis* (7% of all organisms), and *Pseudomonas aeruginosa* (5.5% of all organisms). These were the same organisms reported most commonly for HA UTI cases (Table I).

ANTIMICROBIAL RESISTANCE OF RESPONSIBLE PATHOGENS

Antimicrobial susceptibility tests were performed on a total of 1694 isolates of Gram-positive cocci and 13525 isolates of Gram-negative bacilli. The staphylococcal isolates (*S.aureus*, CoNS) displayed a high resistance to penicillin (73.5%) and erythromycin (65.7%), although there were some differences depending on the species. In this study Staphylococcal isolates showed susceptibility to most of the other antimicrobials tested. Among staphylococcal isolates no strains resistant to linezolid, teicoplanin, vancomycin, tigecycline, and fusidic acid were found. Methicillin-resistance was observed in 8.1% of *S. aureus* (MRSA) and 11.6% CoNS. Streptococcal isolates demonstrated a high resistance against erythromycin (55.6%) and benzylpenicillin (64.8%), followed by ampicillin (31.7%) and tigecycline (16.7%). Most of streptococcal isolates were sensitive to rifampicin (86.3%), clindamycin (89.9%), gentamycin (94.1%), cefuroxime (95.2%), tobramycin (98.9%), and linezolid (99.8%). Regarding the genus Enterococcus, *E. faecalis* isolates were not sensitive to those antibiotics to which they are intrinsically resistant (cefuroxime, clindamycin, and trimethoprim-sulfamethoxazole) and 72.8% of them were resistant to erythromycin. Approximately, 20% of the E. faecalis isolates displayed resistance to high levels of aminoglycosides (gentamycin, tobramycin) and around 11.9% was resistant to quinolones (ciprofloxacin and levofloxacin), and 4.3% to glycopeptides (vancomycin and teicoplanin). Vancomycin resistance was observed in 5.2% of isolated enterococci (VRE). *Enterobacter* spp. was most sensitive (>90%) to ciprofloxacin (97.1%), piperacillin/tazobactam (95.8%), ceftriaxone (93.2%), ceftazidime (93.1%), and fosfomycin (92.1%). No strains resistant to cefepime, meropenem, imipenem, and ertapenem were found. In the present study the most resistant uropathogens were *E. coli, K. pneumoniae, P. mirabilis* and *P. aeruginosa* which showed the high resistance to multiple antibiotics. The overall proportion of extended spectrum beta-lactamases (ESBL) production among *Enterobacteriales* was 25.7%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K. pneumoniae* (33.7%, vs 14.8%, $p < 0.001$). Resistance to third generation cephalosporins was observed in 13.9% *E.coli* isolates and in 10.1% *K. pneumoniae* isolates, respectively. Carbapenem resistance was identified in 13.7% of *P.aeruginosa* isolates. Antibiotic resistance patterns of the most frequent causative uropathogens in pregnant women in Ukraine are presented in Table II.

There was no significant difference in the resistance profile of *E. coli*, *K. pneumoniae, P. mirabilis*, and *P. aeruginosa* across regions or hospital category. Overall, 24.5% of all HA UTI samples were obtained from primary care centers, 35.8% were obtained from secondary care centers, and 39.7% were obtained from tertiary medical centers. The distributions of pathogens were similar within the 3 types of centers (Primary, Secondary and Tertiary). There was no significant difference in resistance profiles from uropathogens between different types of centers (Table III).

DISCUSSION

In the present study, we report the prevalence of UTIs in pregnant women and antimicrobial resistance rates for major causative agents in Ukraine. Although many studies have already described increasing resistance rates in urinary isolates, Ukrainian data are limited either to single centre studies or to studies focusing on resistance to single antibiotic classes. The prevalence of UTIs in pregnant women was 29.5%. Among these patients, 36.5% ASB, 51.7% Cystitis and 11.8% Pyelonephritis were observed. Of all UTI cases 87.9% were defined as HA UTI and 12.1% CA UTI. The prevalence of UTIs in this study was relatively higher compared to findings in other published studies. Other studies report an UTI incidence rate of 10% among pregnant women [2, 3]. It is estimated in pregnant women the incidence of ASB in pregnant women were 2-13% [4,15] and acute cystitis in 1-4% [4,16]. It is reported that acute pyelonephritis may also occur in 0.5-4% of pregnant women [5,17]. Thus, the UTI in pregnant women in Ukraine is much higher than in other countries. In this study, UTIs were polymicrobial. The predominant pathogens were *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*. Our finding was in line with other studies [1, 18, 19]. Our

Table I. Microorganisms causing of Urinary Tract Infections (UTIs) in pregnant women in Ukraine (2020-2022)

Microorganisms	All isolates No. (%)	HA UTI No. (%)	CA UTI No. (%)
Gram-positive cocci	1694 (11.1)	926 (54.7)	768 (45.3)
Enterococcus faecalis	676 (4.4)	397 (58.7)	279 (41.3)
Enterococcus faecium	65 (0.4)	38 (58.5)	27 (41.5)
Streptococcus spp.	306 (2.0)	168 (54.9)	138 (45.1)
CoNS	524 (3.4)	236 (45.0)	288 (55.0)
Staphylococcus aureus	123 (0.8)	87 (70.7)	36 (29.3)
Gram-negative bacilli	13525 (88.5)	11031 (81.6)	2494 (18.4)
Escherichia coli	8280 (54.2)	7369 (89.0)	911 (11.0)
Klebsiella pneumoniae	2166 (14.2)	1708 (78.9)	458 (21.1)
Klebsiella oxytoca	185 (1.2)	88 (47.6)	97 (52.4)
Enterobacter spp.	424 (2.3)	188 (44.3)	236 (55.7)
Proteus mirabilis	1068 (7.0)	699 (65.4)	369 (34.6)
Serratia spp.	189 (1.2)	121 (64.0)	68 (36.0)
Citrobacter spp.	226 (1.5)	133 (58.8)	93 (41.2)
Pseudomonas aeruginosa	847 (5.5)	628 (74.1)	219 (25.9)
Acinetobacter spp.	140 (0.9)	97 (69.3)	43 (30.7)
Fungi	62 (0.4)	29 (46.8)	33 (53.2)
Candida albicans	62 (0.4)	29 (46.8)	33 (53.2)
Total	15281 (100.0)	11986 (78.3)	3295 (21.7)

CoNS, Coagulase-negative staphylococci;
CA UTI, community-acquired urinary tract infection;
HA UTI, healthcare-acquired urinary tract infection

Table II. Resistance pattern of the main causative agents of UTIs in pregnant women in Ukraine (2020-2022)

Pathogen	Antibiotic	HA UTI n/R (%)	CA UTI n/R (%)	P value
Escherichia coli	CRO	7369/857 (11.6)	911/75 (8.2)	<0.001
	CIP	7288/1897 (26.0)	906/153 (16.9)	<0.001
	NOR	7369/2071 (28.1)	877/168 (19.1)	<0.001
	TMP-SMX	2364/648 (27.4)	893/155 (17.4)	<0.001
	FFM	1987/45 (2.3)	902/13 (1.4)	0.018
	AMC	1403/408 (29.1)	897/215 (24.0)	<0.001
	NIT	1276/35 (2.7)	905/15 (1.6)	0.018
Klebsiella pneumoniae	CRO	1708/173 (10.1)	458/29 (6.3)	0.041
	CIP	1627/290 (17.8)	417/48 (11.4)	0.001
	NOR	1588/261 (16.4)	455/54 (11.8)	0.031
	TMP-SMX	1687/221 (13.1)	433/55 (12.7)	0.927
	FFM	1702/488 (28.7)	427/131 (30.7)	0.479
	AMC	1691/301 (17.8)	311/40 (13.0)	0.0412
	NIT	305/206 (67.5)	417/279 (66.9)	0.837
Proteus mirabilis	CRO	588/15 (2.5)	319/6 (1.8)	0.437
	CIP	693/149 (21.5)	347/53 (15.3)	0.05
	NOR	678/147 (21.7)	358/47 (13.1)	0.012
	TMP-SMX	683/209 (30.6)	311/98 (31.5)	0.819
	FFM	654/151 (23.1)	357/62 (17.4)	0.05
	AMC	699/89 (12.7)	369/24 (6.5)	0.012
	NIT	576/576 (100.0)	209/205 (98.8)	0.365
Pseudomonas aeruginosa	CIP	628/92 (14.6)	219/24 (10.9)	0.115
	CEF	581/80 (13.7)	215/17 (7.9)	0.013
	PIP	621/91 (14.6)	207/20 (9.7)	0.041
	CAZ	607/65 (10.7)	211/17 (8.1)	0.252
	IMI	595/82 (13.8)	212/22 (10.4)	0.212

CRO, Ceftriaxone; CIP, Ciprofloxacin; NOR, Norfloxacin; TMP-SMZ, trimethoprim-sulfamethoxazole;
FFM, fosfomycin; NIT, Nitrofurantoin; AMC, Amoxicillin/clavulanic acid; CEF, cefepime; PIP, piperacillin-tazobactam; CAZ, ceftazidime; IMI, Imipenem

study showed that UTI in pregnant women in Ukraine were significantly associated with pathogens resistant to antibiotics. The overall proportion of extended spectrum beta-lactamases (ESBL) production among Enterobacteriaceae was 25.7%. The prevalence of ESBL production among E. coli isolates was significantly higher than in *K.pneumoniae*. Resistance to third-generation cephalosporins was observed in 10.1% *K. pneumoniae* and *E. coli* 13.9% isolates. MRSA was observed in 8.1% of *S.aureus* and 11.6% CoNS. VRE was observed in 5.2% of isolated enterococci. Carbapenem resistance was identified in 13.7% of *P.aeruginosa* isolates. Possibly, higher incidence rate of UTIs in pregnant women in Ukraine were significantly associated with antimicrobial resistance of responsible pathogens. In this study the uropathogens isolated from HA UTI cases were found to be multidrug resistant. These findings correlate with various other studies [1, 11, 15, 18, 19] where multidrug resistant uropathogens were isolated.

The resistance rates of Gram-negative uropathogens to a majority of commonly used antimicrobials in the present study were high, a fact to be expected given the epidemiological situation in the world today. With increasing individual mobility and international travel easier than ever, a global spread of multi-drug-resistant bacterial strains seems an inevitable reality. Increase in the antibiotic resistance amongst the uropathogens indicates that they are hospital acquired and thus difficult to treat. This will be more dangerous if infection prevention practices are not followed during care of the catheterized patients. The chances of transmission of these multi drug resistant are high if health care workers do not follow preventive practices meticulously. In the present study the incidence is much lower because of

Table III. Resistance profile of the main causative agents of HA UTIs in pregnant women in Ukrainian hospitals (2020-2022)

Pathogen	Antibiotic	Hospital category			P value
		Primary n/R (%)	Secondary n/R (%)	Tertiary n/R (%)	
Escherichia coli	CRO	707/78 (11.1)	374/34 (9.1)	233/40 (17.2)	0.0081
	CIP	646/159 (24.7)	333/81 (24.3)	203/66 (32.5)	0.0637
	NOR	711/205 (28.9)	303/83 (27.4)	237/63 (26.6)	0.749
	TMP-SMX	714/183 (25.4)	405/108 (26.7)	306/101 (33.0)	0.0411
	FFM	685/16 (2.3)	412/9 (2.2)	308/7 (2.3)	0.975
	NIT	679/14 (2.1)	392/4 (1.0)	205/7 (3.4)	0.128
	AMC	707/166 (23.5)	384/121 (31.5)	312/121 (38.8)	<0.001
Klebsiella pneumoniae	CRO	213/16 (7.5)	139/10 (7.2)	84/13 (15.5)	0.0642
	CIP	187/29 (15.5)	113/17 (15.0)	70/20 (28.6)	0.0312
	NOR	208/37 (17.8)	100/15 (15.0)	91/12 (13.2)	0.565
	TMP-SMX	199/20 (10.1)	137/17 (12.4)	115/22 (19.1)	0.0631
	FFM	153/30 (19.6)	113/45 (39.8)	75/23 (30.7)	0.001
	NIT	164/115 (70.1)	85/54 (63.5)	56/37 (66.1)	0.547
	AMC	200/29 (14.5)	138/23 (16.7)	120/23 (19.2}	0.535
Proteus mirabilis	CRO	96/1 (1.0)	65/0 (0.0)	47/4 (8.5)	0.0061
	CIP	84/21 (25.0)	49/8 (16.3)	39/8 (20.5)	0.487
	NOR	99/25 (25.3)	44/7 (15.9)	43/8 (18.6)	0.378
	TMP-SMX	97/27 (27.8)	63/18 (28.6)	59/22 (37.3)	0.419
	FFM	70/20 (28.6)	46/9 (19.6)	38/5 (13.2)	0.154
	NIT	98/98 (100.0)	38/38 (100.0)	23/23 (100.0)	-
	AMC	95/7 (7.4)	61/3 (4.9)	60/5 (8.3)	0.654
Pseudomonas aeruginosa	CEF	142/21 (14.8)	100/17 (17.0)	87/7 (8.0)	0.173
	CIP	148/26 (17.6)	123/17 (13.8)	79/8 (10.1)	0.311
	PIP	126/21 (16.7)	130/20 (15.4)	88/9 (10.2)	0.378
	CAZ	152/18 (11.8)	129/14 (10.9)	88/7 (8.0)	0.614
	IMI	139/20 (14.4)	90/13 (14.4)	84/10 (11.9)	0.745

CRO, Ceftriaxone; CIP, Ciprofloxacin; NOR, Norfloxacin; TMP-SMZ, trimethoprim-sulfamethoxazole; FFM, fosfomycin; NIT, Nitrofurantoin; AMC, Amoxicillin/clavulanic acid; CEF, cefepime;
PIP, piperacillin-tazobactam; CAZ, ceftazidime; IMI, Imipenem

continuous monitoring and training of the staff. This is achieved because of the active Infection control team and surveillance for non-compliances.

UTIs are mainly caused by Gram-negative bacteria that are becoming an increasing threat to public health because of their ability to acquire genes, located on transferable plasmids, that code for extended-spectrum β-lactamases (ESBLs). These enzymes are capable of hydrolyzing third-generation cephalosporins and monobactams but not carbapenems. In addition, ESBLs pose a public health problem because they are encoded on plasmids that usually carry other resistance genes against different classes of antibiotics (e.g., aminoglycosides, sulfonamides, and quinolones). As a result, bacteria that acquire these plasmids become multidrug resistant. Although all ESBLs function through cleavage of the amide bond of the β-lactam ring, the genes encoding these enzymes are diverse and grouped into different families. CTX-M type enzymes are the most commonly encountered ESBL types, being present in several members of the order *Enterobacterales* in *P. aeruginosa* and *Acinetobacter* spp. Isolated strains carrying CTX-M confer high-level resistance to cefotaxime and have reduced susceptibility to ceftazidime. Other types of ESBLs are OXAs, AmpCs, and Carbapenemases. OXAs and AmpC are β-lactamase enzymes encoded by chromosomal and plasmid genes that resist inhibition by β-lactamase inhibitors. *K. pneumoniae* carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM-1) are enzymes that make Enterobacteriaceae resistant to a wide range of beta-lactam antibiotics, particularly carbapenemases (CRE) [14, 15]. The most prevalent (TEM + CTX-M) genes were also detected in ciprofloxacin resistant strains *P. mirabilis* and *E. coli* [20]. Because of high prevalence of MDR strains in epidemiologically unrelated patients with AmpC- and/or ESBL producing Proteus spp. infection, further surveillance is needed [21]. Other important mechanisms of resistance are limitation of absorption of a drug, modification of a drug target, and active efflux of a drug. Some bacterial proteins are targets of antimicrobials. Alteration of these bacterial proteins so that the drug binds poorly or does not bind at all is a common mechanism of resistance [19].

We suggest that increased efforts should focus on the prevention and control of hospital infections, and the management of antimicrobial clinical applications to maximize bacterial resistance surveillance. According to literature, antibiotic consumption is a primary driver for AMR, a fact documented on a hospital, regional, and country level [22]. Therefore, the knowledge of local and regional antimicrobial susceptibility patterns is one of the ways to improve antibiotic prescription and at least in part to counter the development of AMR. Monitoring of pathogen resistance profiles is necessary to guide empirical antibiotic therapy before culture and sensitivity results become available. Despite the existence of international guidelines, research shows improper antibiotic prescribing is commonplace [23]. According to a survey from the United States, 30% of primary care antibiotic prescriptions were classified as inadequate. Chardavoyne et al. reported appropriate antibiotic treatment in 68% of adult cystitis cases and 46% of pyelonephritis cases [24]. Treatment in the absence of infection is common and although not recommended in international guidelines for lower UTI management, fluoroquinolones are frequently prescribed.

Our study motivates several potential future areas of research in Ukraine. It would be interesting to examine patterns of resistance in a multi-center study of bacteriuria in pregnant women. Additionally, this work could be expanded to examine antibiotic resistance patterns in other obstetric infections. Finally, in Ukraine data on carbapenem resistance was not available at the time this study was completed. Carbapenem-resistance is an emerging threat identified by the Centers for Disease Control and Prevention, and further investigation into the prevalence of carbapenem-resistant infections in pregnancy is warranted in future work [25].

STRENGTHS AND LIMITATIONS

The biggest strength of this study was the large data set. We analyzed data from 17 regions covering ~70,8% territory of Ukraine. We believe our findings are a solid representation of the current ecology of urinary pathogens in Ukraine. Our data, together with other papers in the literature, complement the picture of AMR worldwide and its trends. Our study provides important new insights into the implications of antibiotic-resistance in pregnancy, but is subject to several limitations. Present study population had a high rate of progression to pyelonephritis which we attributed partially to the inclusion of only culture proven gram negative infections, however differences in clinical practice may also be contributing factors. Data on urine samples collected as a test of cure for initial infections was difficult to collect in a retrospective fashion due to the variable timing of collection and inconsistent documentation. Therefore, rates of cure were not included in this study. The absence of this data makes it difficult to determine whether repeat positive urine cultures were due to re-infection or persistent, or inadequately treated, infection. This limited our ability to assess implications of antibiotic-resistance on obstetric outcomes, such as preterm birth.

CONCLUSIONS

The present study showed that UTIs in pregnant women in Ukraine is a common occurrence and many cases are caused by pathogens that are resistant to antibiotics. Most UTIs in pregnant women are treated empirically with antibiotics, making comprehensive resistance surveillance data essential to guide empiric regimens. A urine culture before initiating antibiotics is essential and the therapy should subsequently be adapted. Multi-faceted interventions, including reinforcement of hand hygiene and control of antibiotic use, are necessary to prevent the spread of MDR uropathogens. Optimizing the management and empirical antimicrobial therapy may reduce the burden of UTIs in pregnant women, but prevention is the key element.

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