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Urinary tract infections in pregnant women and antimicrobial resistance of responsible pathogens in Ukraine: results of a multicenter study (2016-2018)

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SUMMARY

Introduction. Urinary Tract Infections (UTIs) are one of the most common microbial diseases among the pregnant women threat worldwide. However, studies of prevalence of UTIs in the pregnant women in Ukraine are scant. The aim of this study was to obtain the first estimates of the current prevalence of UTIs in the pregnant women and antimicrobial resistance of responsible pathogens in Ukraine.

Materials and Methods. We performed a retrospective multicenter cohort study. The study population consisted of 27,388 pregnant women from 9 regions of Ukraine. Microbial isolates were identified using standard microbiological techniques, including automated microbiology testing. Isolates were categorized as susceptible or resistant by Clinical and Laboratory Standards Institute criteria.

Results. Total 24.3% pregnant women were found to have UTIs. Among these patients, 57.5% Asymptomatic bacteriuria, 35% Cystitis and 7.6% Pyelonephritis were observed. The predominant pathogens were: *Escherichia coli* (36.2%), *Enterococcus faecalis* (19.5%), *Klebsiella pneumoniae* (11.1%), *Enterobacter* spp. (7.2%), *Pseudomonas aeruginosa* (6.4%), and *Proteus* spp. (4.2%). The overall proportion of methicillin-resistance was observed in 11.2% of *Staphylococcus aureus* (MRSA). Vancomycin resistance was observed in 3.2% of isolated enterococci. Carbapenem resistance was identified in 6.3% of *P.aeruginosa* isolates. Resistance to third-generation cephalosporins was observed in 9.7% *Klebsiella* spp. and *E.coli* 12.8% isolates. The overall proportion of extended spectrum beta-lactamases (ESBL) production among Enterobacteriaceae was 24.8%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K. pneumoniae* (34.1%, vs 11.7%).

Conclusions. A UTIs in the pregnant women in Ukraine is a common occurrence and many cases are caused by pathogens that are resistant to antibiotics. Given of the rapidly developing antimicrobial resistance, the policy of antibiotic use for UTIs treatment in each region should be determined depending on local data on resistance to antimicrobials.

Key words: pregnant women; urinary tract infection; asymptomatic bacteriuria; cystitis; pyelonephritis; antimicrobial resistance

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INTRODUCTION

Urinary Tract Infections (UTIs) are the most common type of infection during pregnancy [1]. UTIs are the most common type of infection during pregnancy, affecting up to 10% of pregnant women [1,2]. The spectrum of UTIs ranges from lower urinary tract disease (asymptomatic bacteriuria, acute cystitis) to upper urinary tract disease (acute pyelonephritis). It is estimated in pregnant women the incidence of Asymptomatic Bacteriuria (ASB) in pregnant women were 2-13% and acute cystitis in 1-4% [3]. It is reported that acute pyelonephritis may also occur in 1-4% of pregnant women [4].

It is reported that the development of UTIs in pregnant women can lead to complications in maternal and fetal complications such as preterm labor, low birth weight, or maternal systemic infection [2]. It is estimated that every tenth pregnant women with pyelonephritis will eventually go into preterm labor [5]. Untreated UTIs in pregnant women may increase the risk of fetal developmental alterations and mental retardation [6]. In addition, UTIs is closely associated with a higher risk of premature rupture of the membranes, premature birth and early neonatal systemic infection [3,7]. 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. Optimally, the given antibiotic should be selected depending on the safety profile and local drug susceptibility. However, in Ukraine, there is no national network for the UTIs surveillance. The previous reports of UTIs in Ukraine have been limited only to Healthcare-Associated Infections (HAIs) [8,9].

THE AIM

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

MATERIAL AND METHODS

Study design and participants

We performed a retrospective multicenter cohort study. The study population consisted of 27,388 pregnant women from 9 regions of Ukraine. To be included in the study, pregnant women must local residents. Women's were excluded if they were not a local resident of the selected regions. In addition, local women were excluded from the study if they did not regularly visit doctors and medical records were not properly executed. In total of 27 women were excluded from the study.

Data collection

Information on UTIs was collected at baseline and each follow-up visit. The first urine sample was taken at the first visit to the doctor. All women visited a doctor till the onset of labor. The interval between visits to the doctor was 2 weeks, but a urine sample was taken from pregnant women one time per trimester. Full-text ambulatory medical records and relevant hospital records were reviewed for the all pregnancy period women's. All free-text notes were reviewed, and encounters for which the principal focus was the UTIs were identified. 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.

Definition

In pregnant women 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. The UTIs in pregnancy are by definition considered complicated infections. Urine samples showing a colony count more than 105 cfu/mL were considered to be positive for UTI.

Microbiological sampling and susceptibility testing

We analyzed urine samples from pregnant women's in the context of a study about microbiology of UTIs and antimicrobial resistance of responsible pathogens. Urine samples were obtained from pregnant women with clinical symptoms of UTIs. Results were not considered for more than two clinical isolates obtained from the same patient and the sample was considered to be contaminated. Microbial isolates were identified using standard microbiological techniques, including automated microbiology testing (Vitek-2; bioMe´rieux, Marcy l'Etoile, France), and antibiotic susceptibility testing was performed by using the disk diffusion method. Isolates were categorized as susceptible or resistant by Clinical and Laboratory Standards Institute criteria (CLSI, 2013) [10]. Strains in the intermediate range were classified as resistant for data analysis.

Ethics

The Shupyk National Medical Academy of Postgraduate Education (Kyiv, Ukraine) ethics committee approved the waiver of informed consent to participate in this study due to its retrospective design. All pregnant women's data were anonymised prior to the analysis.

Statistical analysis

The incidence 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 (Microsoft Corp., Redmond, WA, USA). 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 utis in pregnant women

During the study period (January 1st, 2016 and December 31st, 2018), 6,652 of 27,388 pregnant women's were found to have UTIs. The incidence of UTIs was 24.3% [95% CI 24%, 24.6%, P<0.0001]. Among these cases, 57.5% (3,823/6,652) asymptomatic bacteriuria, 35% (2,326/6,652) cystitis, and 7.6% (503/6,652) pyelonephritis were observed. The incidence of type of UTIs in pregnant women's differed according to the regions of Ukraine (Tab.1). Demographic characteristics pregnant women with UTI are presented in Tab.2.

Microorganisms causing of utis in pregnant women

In this study, a total of 19,274 urine samples from pregnant women suffering UTIs were analyzed using culturebased methods. Among the 19,274 analyzed samples, 40.5% (7802/19,274) samples did not show any microbial growth. The remaining 59.5% (11472/19274) samples were positive for uropathogens with colony count higher than 104 CFU/mL of urine and were included in the current study analysis. Aerobic gram-negative bacilli make up 67% (7,638/11,472) and 30.9% (3,545/11,472) gram-positive cocci from of all isolates. In this study, 22.3% UTIs were polymicrobial.

The predominant pathogens of UTIs were: *Escherichia coli* (36.2%), *Enterococcus faecalis* (19.5%), *Klebsiella pneumoniae* (11.1%), Enterobacterspp. (7.2%), *Pseudomonas aeruginosa* (6.4%), and *Proteus* spp. (4.2%). They are closely followed by Coagulase-negative staphylococci (3.1%), streptococci (3%), *Staphylococcus aureus* (2.8%), *Enterococcus faecium* (2.5%), *Candida albicans* (2.1%), *Citrobacter* spp. (0.6%), *Klebsiella oxytoca* (0.5%), *Serratia* spp. (0.5%), *Acinetibacter* spp. (0.4%). The

Tab. 1. Distribution of type of urinary tract infections (UTIs) in pregnant women in Ukraine

Region	All women's No.	Type of UTIs*			Total of UTIs No. (%) of cases
		ASB** No. (%) of cases	Cystitis No. (%) of cases	Pyelonephritis No. (%) of cases	
A	4854	676 (13.9)	479 (9.9)	118 (2.4)	1273 (26.2)
B	3824	435 (11.4)	307 (8.0)	44 (1.2)	786 (20.6)
C	2792	332 (11.9)	232 (8.3)	33 (1.2)	597 (21.4)
D	2715	428 (15.8)	231 (8.5)	52 (1.9)	711 (26.2)
E	2687	322 (12.0)	215 (8.0)	31 (1.2)	568 (21.1)
F	2642	372 (14.1)	263 (10.0)	57 (2.2)	692 (26.2)
G	2631	397 (15.1)	141 (5.4)	29 (1.1)	567 (21.6)
H	2632	462 (17.6)	247 (9.4)	72 (2.7)	781 (29.7)
I	2611	399 (15.3)	211 (8.1)	67 (2.6)	677 (25.9)
Total	**27388**	**3823 (14.0)**	**2326 (8.5)**	**503 (1.8)**	**6652 (24.3)**

*UTIs, Urinary Tract Infections; **ASB, Asymptomatic bacteriuria

Tab.2. Patient demographics (Age) in pregnant women in Ukraine

Characteristics	All pregnant women's		UTIs				*P* value	Prevalence of UTIs % [95% CI]
			No		Yes			
	n	%	n	%	n	%		
All	27388	100	20736	75.7	6652	24.3	0.0001	24.3 [24.0 – 24.6]
Age								
16-18 years	584	2.1	208	35.6	376	64.4	0.0001	64.4 [59.4 – 71.4]
19-21 years	2216	8.1	838	37.8	1378	62.2	0.0001	62.2 [56.5 – 69.0]
22–24 years	4612	16.8	3381	73.3	1231	26.7	0.0001	26.7 [25.6 – 27.9]
25–27 years	6638	24.2	5280	79.5	1358	20.5	0.0001	20.5 [19.8 – 21.3]
28–30 years	8827	32.2	7549	85.5	1278	14.5	0.0001	14.5 [14.1 – 14.9]
31-33 years	1406	5.3	1148	81.6	258	18.4	0.0001	18.3 [17.8 – 19.1]
34-36 years	641	2.3	530	82.7	111	17.3	0.0001	17.3 [16.8 – 18.1]
37-39 years	618	2.3	512	82.8	106	17.2	0.0001	17.2 [16.6 – 17.9]
40-42 years	501	1.8	409	81.6	92	18.4	0.001	18.4 [17.8 – 19.2]
43-45 years	322	1.2	260	80.7	62	19.3	0.034	19.3 [18.7 – 20.2]
46-48 years	451	1.7	319	70.7	132	29.3	0.012	29.3 [28.2 – 30.9]
49-51 years	388	1.4	244	62.9	144	37.1	0.0001	37.1 [35.6 – 39.4]
≥52 years	184	0.7	58	31.5	126	68.5	0.0001	68.5 [63.4 – 77.9]

distribution of the microorganisms differed according to the UTIs types (Tab.3).

Antimicrobial resistance of responsible pathogens

Antimicrobial susceptibility tests were performed on a total of 3545 isolates of Gram-positive cocci. The staphylococcal isolates displayed a remarkable resistance to penicillin (87.3%) and erythromycin (68.6%), although there were some differences depending on the species. Staphylococcal isolates showed susceptibility to most of the other antimicrobials tested. No strains resistant to linezolid, teicoplanin, vancomycin, tigecycline, and fusidic acid were found. Methicillin-resistance was observed in 11.2% of *S. aureus* (MRSA) and 9.4% CoNS.

Streptococcal isolates demonstrated a noteworthy resistance against erythromycin (68.7%) and benzylpenicillin (63.7%), followed by ampicillin (31.5%) and tigecycline (18.8%). Most of the 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 (n = 2236) were not sensitive to those antibiotics to which they are intrinsically resistant (cefuroxime, clindamycin, and trimethoprim-sulfamethoxazole) and 83.7% of them were resistant to erythromycin. Approximately, 20% of the *E. faecalis* isolates displayed resistance to high levels of aminoglycosides (gentamycin, tobramycin) and around 7.9% was resistant to quinolones (ciprofloxacin and levofloxacin), and 4% to glycopeptides (vancomycin and teicoplanin). Vancomycin resistance was observed in 3.2% of isolated enterococci (VRE).

The overall proportion of extended spectrum betalactamases (ESBL) production among Enterobacteriaceae was 24.8%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K. pneumoniae* (34.1%, vs 11.7%, $p < 0.001$). *E.coli* was most sensitive (>90%) to ertapenem (100%), cefotaxime (99.1%), ceftazidime (99.4%), fosfomycin (98.7%), imipenem (98.9%), piperacillin/tazobactam (97.3%), and gentamycin (94.5%) but least susceptibility (<70%) was observed for moxifloxacin (54.2%), cefuroxime (61.8%), amoxicillin (65.2%), and levofloxacin (67.3%). Resistance to third-generation cephalosporins was observed in 12.8% *E.coli* isolates. No strains resistant to ertapenem were found.

Enterobacter spp. was most sensitive (>90%) to ciprofloxacin (97.1%), piperacillin/tazobactam (95.8%), cefotaxime (95.1%), ceftazidime (94.8%), ticarcillin (92.7%), and fosfomycin (92.1%). No strains resistant to cefepime, meropenem, imipenem, and ertapenem were

Tab. 3. Microorganisms causing of UTIs in pregnant women in Ukraine (2016-2018)

Microorganisms[a]	All isolates No. (%)	No. (%) of isolates		
		ASB[b]	Cystitis	Pyelonephritis
Gram-positive cocci	**3545 (30,9)**	**1773 (35,7)**	**1275 (32,1)**	**497 (19,6)**
Enterococcus faecalis	2236 (19,5)	1136 (22,9)	896 (22,6)	204 (8,0)
Enterococcus faecium	287 (2,5)	117 (2,4)	38 (1,0)	132 (5,2)
Streptococcus spp.	343 (3,0)	144 (2,9)	122 (3,1)	77 (3,0)
CoNS[c]	358 (3,1)	234 (4,7)	83 (2,1)	41 (1,6)
Staphylococcus aureus	321 (2,8)	142 (2,9)	136 (3,4)	43 (1,7)
Gram-negative bacilli	**7638 (67,0)**	**3074 (62,0)**	**2574 (64,8)**	**2033 (80,0)**
Enterobacteriaceae	6903 (60,2)	2929 (59,0)	2245 (56,5)	1729 (68,1)
Escherichia coli	4153 (36,2)	2011 (40,5)	1266 (31,9)	876 (34,5)
Klebsiella pneumoniae	1272 (11,1)	401 (8,1)	448 (11,3)	423 (16,7)
Klebsiella oxytoca	55 (0,5)	28 (0,6)	27 (0,7)	0
Enterobacter spp.	825 (7,2)	301 (6,1)	321 (8,1)	203 (8,0)
Proteus spp.	479 (4,2)	102 (2,1)	160 (4,0)	217 (8,5)
Serratia spp.	52 (0,5)	30 (0,6)	12 (0,3)	10 (0,4)
Citrobacter spp.	67 (0,6)	56 (1,1)	11 (0,3)	0
Non-fermenting gram-negative bacteria	778 (6,8)	145 (2,9)	329 (8,3)	304 (12,0)
Pseudomonas aeruginosa	735 (6,4)	124 (2,5)	321 (8,1)	290 (11,4)
Acinetobacter spp.	43 (0,4)	21 (0,4)	8 (0,2)	14 (0,6)
Fungi	**246 (2,1)**	**114 (2,3)**	**122 (3,1)**	**10 (0,4)**
Candida albicans	246 (2,1)	114 (2,3)	122 (3,1)	10 (0,4)
Total no. of isolates	**11472**	**4961**	**3971**	**2540**

Notes:
(a) Used "The Bergey's Manual of Determinative Bacteriology" 9th Edition
(b) ASB: Asymptomatic bacteriuria
(c) CoNS: Coagulase-negative staphylococci

found. *Enterobacter* spp. isolates ones exhibited a noticeable percentage of resistance against ampicillin/sulbactam (61.9%), amoxicillin/clavulanic acid (60.2%), ciprofloxacin (47.8%), clindamycin (52.2%), ampicillin (52.1%), amikacin (43.8%), and gentamycin (43.5%), cefaperazon (41.3%) and ceftriaxon (34.1%).

K. pneumoniae isolates showed susceptibility to most of the other antimicrobials (meropenem, imipenem, levofloxacin, and gentamycin) tested, while these isolates ones exhibited a noticeable percentage of resistance against ampicillin (51.5%), amoxicillin/clavulanic acid (41.4%), ofloxacin (33.1%), and ciprofloxacin (29.7%). No strains resistant to piperacillin/tazobactam and ertapenem were found. Resistance to third generation cephalosporins was observed in 9.7% *K. pneumoniae* isolates. *Proteus* spp. was most sensitive (>90%) to imipenem (97.3%), gentamycin (96.4%), cefotaxime (94.7%), cefepime (94.3%), and ceftazidime (91.2%). No strains resistant to ertapenem piperacillin/tazobactam, and amikacin were found. In our study *P. aeruginosa* isolates demonstrated remarkable resistance to cefepime (49.1%), gentamycin (35.9%), and cefoperazone (33.8%), and was most sensitive to meropenem (97.2%), imipenem (88.6%), piperacillin/tazobactam (87.8%), ceftazidime (88.1%), amikacin (85.1%), ticarcillin (81.9%), ciprofloxacin (81.9%). No strains resistant to ertapenem were found. Carbapenem resistance was identified in 7.3% of *P.aeruginosa* isolates.

DISCUSSION

This study presents the first epidemiological multicenter cohort study for current prevalence of UTIs among pregnant women and antimicrobial resistance of responsible pathogens in Ukraine.

During the study period (2016-2018) the prevalence of UTIs in pregnant women was 24.3%. Among these patients, 57.5% ASB, 35% Cystitis and 7.6% Pyelonephritis were observed. Other studies report an UTI incidence rate of 10% among pregnant women [1,2]. It is estimated in pregnant women the incidence of ASB in pregnant women were 2-13% [3,11,12] and acute cystitis in 1-4% [3,13]. It is reported that acute pyelonephritis may also occur in 0.5-4% of pregnant women [4,14,15]. Thus, the UTI in pregnant women in Ukraine is much higher than in other countries. Possibly this is due to the presence of many risk factors among pregnant women in Ukraine.

In this study, 22.3% UTIs were polymicrobial. The predominant pathogens were *E. coli* (36.2%), *E. faecalis* (19.5%), *K. pneumoniae* (11.1%), *Enterobacter* spp. (7.2%), *P. aeruginosa* (6.4%), and *Proteus* spp. (4.2%). They are closely followed by CoNS (3.1%), streptococci (3%), *S. aureus* (2.8%), *E. faecium* (2.5%), *C. albicans* (2.1%), *Citrobacter* spp. (0.6%), *K. oxytoca* (0.5%), *Serratia* spp. (0.5%), *Acinetibacter* spp. (0.4%). It is estimated, urine culture samples during pregnancy contain predominantly similar pathogens [3,4,16].

Our study showed that UTI in pregnant women in Ukraine were significantly associated with pathogens resistant to antibiotics. The overall proportion of extended spectrum betalactamases (ESBL) production among Enterobacteriaceae was 24.8%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K.pneumoniae* (34.1%, vs 11.7%). Resistance to third-generation cephalosporins was observed in 9.7% *K. pneumoniae* and *E. coli* 12.8% isolates. Methicillin resistance was observed in 11.2% of *S.aureus* (MRSA) and 9,4% CoNS. Vancomycin resistance was observed in 3.2% of isolated enterococci (VRE). Carbapenem resistance was identified in 7.3% of *P.aeruginosa* isolates. Possibly, higher incidence rate of UTIs in pregnant women in Ukraine were significantly associated with many risk factors and antimicrobial resistance of responsible pathogens.

The most of antimicrobials cross the placenta, and some of them may exert teratogenic effects [17]. In all patients antibiotics should be given, for at least the first 48 h. Antibiotic therapy is usually continued for 10–14 days [18]. However, as of today, there is insufficient data to recommend specific treatment regimens for pregnant women. ß-lactam antibiotics are used most commonly, as they are relatively safe for the fetus. The results of the studies on perinatal outcomes of untreated ASB are controversial. Although a number of them demonstrated a relationship of ASB in pregnant mothers and the risk of premature delivery, some other studies failed to prove the association [19,20].

According to the literature, maternal bacteriuria in a pregnant woman is considered a marker for genital tract colonization with this organism [21]. Urine culture remains the most reliable test allowing the diagnosis of ASB. However, to date, the question has not been resolved: should women in whom no ASB was detected upon the first examination have addi-

tional screening in later pregnancy? [22]. Our study showed that repeating the urine culture in each trimester improves the detection rate of ASB.

CONCLUSIONS

The study showed that UTIs in the pregnant women in Ukraine is a common occurrence and many cases are caused by pathogens that are resistant to antibiotics. Given of the rapidly developing antimicrobial resistance, the policy of antibiotic use for UTIs treatment in each region should be determined depending on local data on resistance to antimicrobials. Optimizing the management and empirical antimicrobial therapy may reduce the burden of UTIs, but prevention is the key element. This investigation provides valuable data as a first study for national surveillance of UTIs and potential comparison with data from other countries.

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