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Pyuria, bacteriuria and empirical antibiotic selection in pregnant women

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ABSTRACT

Aims: In pregnancy, early diagnosis and proper treatment of urinary tract infections are crucial in preventing maternal and fetal comorbidities. Therefore, pregnant women should be screened for asymptomatic bacteriuria. This study aimed to evaluate the relationship between pyuria and bacteriuria and the susceptibility of uropathogens, as well as to review the empiric drug options for pregnant women.

Methods: The presence of pyuria and bacteriuria in urine samples obtained from the pregnant outpatient clinic between January 2023 and December 2023 at Kırıkkale University Faculty of Medicine Hospital's Infectious Diseases and Clinical Microbiology Laboratory was investigated. Uropathogens were identified and typed using the BD Phoenix™ M50 automated system for bacterial identification and antibiotic susceptibility testing, and antibiotic susceptibility was interpreted according to the European Committee on Antimicrobial Susceptibility Testing criteria.

Results: A total of 1457 urine samples were evaluated in this retrospective study. Uropathogens were detected in 235 patients, while 301 samples were considered contaminated. Uropathogens were found to be susceptible to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, nitrofurantoin, and fosfomycin, in that order, for use in pregnant women. High resistance rates to third-generation cephalosporins were observed.

Conclusion: According to the results of this study, local resistance rates against urinary pathogens in pregnant women should be determined at specific intervals, and empirical antibiotic therapy should be planned based on these data.

Keywords: Asymptomatic bacteriuria, urinary tract infection, empirical antibiotherapy

INTRODUCTION

Urinary tract infections (UTIs) are common infections during pregnancy. In addition to conventional UTIs (acute cystitis and acute pyelonephritis), asymptomatic bacteriuria (ASB) is also among the diseases that should be treated in pregnancy.[1]

ASB is more common in people under the age of 20, nulliparous, at risk of bacteriuria, with previous urinary tract infections, sickle cell anemia, diabetes diagnosis, smoking history and low socioeconomic status, especially in the first trimester of pregnancy.[2-4] There are publications showing that ASB in pregnant women leads to upper UTI such as pyelonephritis in the absence of treatment.[5]

Some studies have shown a positive correlation between the presence of untreated bacteriuria in pregnant women and the risk of preterm delivery, low birth weight and perinatal mortality.[6] In pregnant women with pyelonephritis, obstetric outcomes such as increased preterm delivery rate and complications such as anemia, acute respiratory failure and sepsis that increase maternal morbidity can be seen regardless of the trimester.[4,7,8]

There is no difference in virulence between uropathogens seen in pregnancy and uropathogens seen in non-pregnant individuals. However, the ability of bacteria to move ascending may increase due to relaxation of smooth muscles and dilatation of the ureter due to pregnancy. This is thought to be the main reason why a non-symptomatic bacteriuria is a risk factor for pyelonephritis in pregnant women.[9] In addition, immunosuppression such as a decrease in mucosal interleukin 6 levels due to pregnancy may occur.[10]

Pregnant women should be screened for bacteriuria at least once regardless of the presence of symptoms to prevent fetal and maternal complications. Screening should be repeated in pregnant women with risk factors for UTI.[2] The Infectious Diseases Society of America (IDSA) defines ASB as the detection of 10 colonies/ml or more of the same bacterial strain in two consecutive measurement.[11] However, this definition is based on studies in non-pregnant women. ACOG (American College of Obstetricians and Gynaecologists) recommends screening for ASB by urine culture once in

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pregnant women.[12] In some studies, it has been reported that growth in a single culture is sufficient for treatment decision for group B streptococci in pregnant women.[13] In most patients with infection, the urine in the bladder usually contains at least 10 CFU/ml. However, one third of young women with cystitis may have less than 10 CFU/ml of bacteria. In such women, low numbers of *Enterobacteriaceae* (i.e. 10 -10 CFU/ml) are highly associated with infection.[14] The IDSA consensus culture definition for cystitis is ≥10 CFU/ml and for pyelonephritis ≥10 CFU/ml.[15]

Potential agents that can be given to pregnant women are beta-lactams, nitrofurantoin and fosfomycin. However, the resistance mechanisms encountered in bacteria and the fact that the optimal duration of treatment is not specified with precise criteria bring failure in the treatment of bacteriuria.[16] In this study, the presence of pyuria and bacteriuria in urine samples obtained from pregnant women was investigated, samples with pyuria were compared with culture results and the susceptibility of antimicrobial options (available for pregnant women) were examined. It was aimed to review the empirical treatment regimen to be chosen for pregnant women and to avoid the use of antibiotics with high resistance rates.

METHODS

The study was carried out with the permission of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 20.12.2023, Decision No: 2023.12.15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, 1457 urine samples obtained from patients who applied to the pregnant outpatient clinic between January 2023 and December 2023 were included in our laboratory. Samples with at least 10 leukocytes/ml in the leukocyte counting chamber were considered pyuric. All incoming samples were inoculated with 0.01 milliliter aliquots on 5% sheep blood agar and eosine methylene blue agar (EMB) media and incubated for 24-48 hours at 35-37˚C in aerobic environment. At the end of incubation, the plates were evaluated and more than 10 colonies/ml were considered to be significant and studied with BD Phoenix™ M50 bacterial identification and antibiotic susceptibility system. Antibiotic susceptibility was interpreted according to the European Committee on Antimicrobial Susceptibility Testing criteria.[17] Amoxicillin-clavulonate, 3rd generation cephalosporin, trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin and fosfomycin, which are recommended for use in pregnant women, were evaluated in susceptibility results. Urine samples in which three or more types of bacteria are detected without a predominant microorganism are considered contaminated.[18]

RESULTS

Between the specified dates, 1457 midstream urine samples were sent to our laboratory for culture, excluding duplicate samples from the pregnant outpatient clinic. Pyuria was detected in 298 (20.45%) of the samples and significant growth was observed in 235 (16.1%). 227 (15.57%) were considered as contamination because they were polymicrobial. The values of pyuria detected in urine were between 10-2000 leukocytes/ml. The relationship between the amount of pyuria and growth is shown in Table 1.

Escherichia coli (E. coli) was detected in 64 (27%) of 235 samples. The second most frequently isolated agent was group *B. streptococcus* with 54 (22%). Among the agents, 193 (82%) were susceptible to amoxacillin+clavulonate, 167 (71%) to TMP-SMX, 113 (48%) to nitrofurantoin and 169 (72%) to cephalosporin resistance. The susceptibilities for the causative agents are shown in Table 2.

Table 1Pyuria-bacteriuria relationship

	No cell n (%)	10-49 leukocytes/ml n (%)	50-99 leukocytes/ml n (%)	100-2000 leukocytes/ml n (%)	Total n (%)
No reproduction	779 (0.53)	119 (0.08)	0 (0)	33 (0.02)	921 (63)
Contamination	227 (0.16)	62 (0.04)	12 (0.01)	0 (0)	301 (0.20)
Bacteriuria	153 (0.11)	40 (0.03)	42 (0.03)	16 (0.01)	235 (0.16)
Total	1159 (0.8)	221 (0.15)	54 (0.04)	49 (0.03)	1457 (100)

Table 2 Agent-sensitivity ratios

	Amoxicillin+clavulonate n (%)	Cephalosporin n (%)	Fosfomycin n (%)	Nitrofurantoin n (%)	SXT n (%)	Total n (%)
Enterococcus spp.	14 (100)	0 (0)	10 (71)	6 (43)	0 (0)	14 (100)
Klebsiella spp.	57 (100)	23 (40)	36 (63)	55 (96)	47 (82)	57 (100)
Escherichia coli	22 (34)	43 (67)	43 (67)	22 (34)	25 (39)	64 (100)
Coagulase negative *Staphylococcus*	46 (100)	0 (0)	20 (43)	30 (65)	41 (89)	46 (100)
Streptecoccus agalactia	54 (100)	0 (0)	0 (0)	0 (0)	54 (100)	54 (100)
Total	193 (82)	66 (28)	109 (46)	113 (48)	167 (71)	235 (100)

DISCUSSION

UTI is one of the most common infectious diseases in the community. Urinary tract infections in the female gender show a bimodal course and peak in sexually active women aged 15-24 years and postmenopausal women.[19,20] It is estimated that 10-12% of women experience UTI at least once a year.[21] In studies conducted in pregnant women, no difference was found between different antibiotic regimens in terms of cure rate, incidence of recurrent infection, preterm delivery and antibiotic change.[22] However, especially in untreated UTIs, empirical treatment should be initiated rapidly due to the possibility of complications.[5]

E. coli is the most common uropathogenic agent.[23] In this study, *E. coli was* the most common agent detected in pregnant women. However, in the last two decades, an increasing resistance pattern against *E. coli* has been observed worldwide. Increasing resistance rates are observed especially against agents frequently used in treatment such as fluoroquinolones and TMP-SMX.[23,24] Since these two agents are considered among group C. antimicrobials in pregnant women, the importance of beta lactam susceptibility increases. In recent years, extended spectrum beta lactamase (ESBL) production even in community-acquired *E. coli* strains has become an important problem in treatment.[25] In ESBL-producing strains, oral treatment options decrease, treatment failure, hospitalization rates and treatment costs increase.[26,27] The high level of cephalosporin resistance in this study suggests that the number of oral agents that can be selected for pregnant women will decrease in the future.

Penicillins (including beta-lactamase inhibitors), cephalosporins, carbapenems (ertapenem and meropenem), aztreonam and fosfomycin are safe agents for use in pregnant women.[28] Therefore, considering the broad spectrum of activity, 3rd generation cephalosporins, amoxicillin-clavulanate or fosfomycin are recommended for outpatient and oral treatment in non-invasive UTIs such as acute cystitis and ASB. Nitrofurantoin and TMP-SMX are considered first-line agents in cases of allergy/resistance where other agents cannot be used in the first trimester and in the 2-3rd trimesters.[29] However, since nitrofurantoin has been associated with fetal hemolytic anemia when used at 38-42 weeks of gestation, it is recommended that priority be given to other agents if possible.[30,31]

As a result of this study, it is recommended that amoxicillin-clavulanate with 82% sensitivity in all lower and upper UTIs should be selected as the most effective agent in empirical treatment for pregnant women in our region. The other agent of choice for upper UTI is TMP-SMX with 75% sensitivity. For lower UTI, nitrofurantoin with a sensitivity of 48% and fosfomycin with a sensitivity of 46% are considered to be the agents that should be selected for targeted treatment according to the sensitivity results instead of empirical treatment. Due to the resistance seen in our region, empirical use of 3rd generation cephalosporins should be avoided, and they should be kept in reserve as the agent of choice in the presence of resistance to other agents.

In a study evaluating the presence of pyuria and culture results, the causative agent could be produced in 34% of women with pyuria.[32] In this study, this rate was 27.5%. The causes of sterile pyuria may include antibiotic use, infection with bacteria that are difficult to grow, growth of less than 10 colonies excluded in culture, urethritis agents, presence of contamination or diuresis.[33] Therefore, it is recommended that pyuria should not be used alone in the diagnosis of UTI in pregnant women.

After ASB screening became routine, the incidence of pyelonephritis in pregnancy decreased from 20-35% to 1-4%.[2] Repeated screening is not recommended in pregnant women after a first negative screening as the risk of pyelonephritis is low.[34] ASB is significant in bacterial growths of 10 CFU/ml and above. Lower growths should be considered as vulvovaginal contamination and treatment should be avoided.[35] In all treatments except fosfomycin, 5-7 daily doses have been shown to be superior to a single dose.[36,37] Antimicrobial agents should be started immediately after bacteriuria is demonstrated, and if necessary, a change of treatment should be considered according to the susceptibility result.[31] In this study, we recommend fosfomycin, which has high efficacy in all uropathogens, as the first agent to be given in asymptomatic treatment, especially because it is effective in single dose use. In case of fosfomycin resistance, other agents should be considered for at least 5 days.

Contamination rates may be higher during pregnancy than in the normal population due to difficulty in capturing midstream urine.[38] In this study, this rate was 21%. However, there is no specific evidence for repeating the sample in the presence of contamination. Since contamination of skin flora elements was detected in one third of pregnant patients, sample repetition may not be successful in ruling out contamination.[38]

Limitations

The most important limitation of the study is that it included patients from a single center. Since it was a retrospective laboratory study, information about the patients' background and family history such as recent antibiotic use, hospitalization history, comorbid diseases could not be evaluated. *In vitro* susceptibilities of uropathogens were evaluated and *in vivo* activities were excluded.

CONCLUSION

Determination of local epidemiology and antibiotic susceptibilities is the most fundamental step in the fight against infection. Therefore, resistance rates against urinary pathogens should be determined at certain times and empirical antibiotic therapy should be planned according to these data. According to this study, it is recommended to prefer amoxicillin-clavulonate in the presence of symptomatic UTI and fosfomycin in ASB for empirical antibiotherapy in pregnant women, and to revise the treatment if necessary according to the results of the factor.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 20.12.2023, Decision No: 2023.12.15). This study was presented as an oral presentation at the 7th International Antalya Congress.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the study and that they have approved the final version.

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