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Antibiograms of uropathogens in obstetric patients

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Background: Urinary tract infections (UTI) are the most commonly encountered infections in obstetric patients. Aim: The current study was undertaken to find the spectrum of micro-organisms responsible for causing UTI in obstetric patients and to find out the most appropriate antibiotic. **Materials and Methods:** Consecutive patients in different stages of pregnancy with or without symptoms of UTI attending the antenatal clinic from June 2019 to November 2020 were screened for significant bacteriuria. The bacterial uropathogens isolated were then subjected to antimicrobial susceptibility testing and screened for ESBL production and methicillin resistance. **Results:** During the 18-month study period, out of the 110 samples screened, a total of 66 (60%) samples of urine from pregnant females, in different stages of pregnancy were found to be positive on culture. The Enterobacteriaceae accounted for nearly 69.69% of the isolates and E. coli alone accounted for 42.42% of the urinary isolates followed by Acinetobacter 19.69%. Among the Gram-positive cocci, Enterococcus 25.75% were more frequently isolated than Staphylococcus aureus (4.54%). Significantly high resistance was noted to the beta-lactam group of antimicrobials, fluoroquinolones and cotrimoxazole, both by the Gram-negative bacilli as well as Gram-positive cocci. Resistance was quite low against the aminoglycosides and nitrofurantoin and virtually absent against imipenem. **Conclusion:** The susceptibility patterns seen in our study seem to suggest that it is necessary to obtain sensitivity reports before initiation of antibiotic therapy in cases of suspected UTI.

Keywords: ESBL, Pregnancy, Urinary tract infection, Uropathogens

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Introduction

Urinary tract infections (UTI) are the most commonly encountered infections in obstetric patients. They can be classified as either asymptomatic or symptomatic. Asymptomatic bacteriuria (ASB) is defined as the presence of significant bacteriuria without the symptoms of an acute UTI and is reported to be seen in around 5-10% of pregnancies. Symptomatic UTIs are divided into the lower tract, acute cystitis, affecting 1-3% of patients, or upper tract, (acute pyelonephritis) which complicates 0.5-1.5% of the pregnancies. Most cases of pyelonephritis are sequelae of untreated, recurrent or inadequately treated lower UTI. [1,2]

Pregnant women diagnosed with ASB or acute cystitis are often treated empirically before the results of culture and antibiotic sensitivity are available. Although a variety of etiology is involved, E. coli and other coliforms account for a large majority of these naturally acquired infections. [2,3] Rapid evaluation and treatment of UTI are important to prevent renal parenchymal damage and renal scarring that can cause hypertension and progressive renal damage (4). The emergence and spread of antimicrobial resistance is a cause of increasing concern (5).

It is one of the major causes of failure in the treatment of infectious diseases that result in increased morbidity, mortality, and economic burden (6). Since most UTIs are treated empirically the selection of antimicrobial agent should be determined not only by the most likely pathogen but also by its expected susceptibility pattern. Thus, knowledge of local antimicrobial susceptibility patterns of common uropathogens is essential for prudent empiric therapy of community-acquired UTIs.

Thus the present study was carried out to determine the spectrum of bacterial isolates causing UTI and their antibiotic susceptibility among pregnant women attending antenatal clinic.

Materials and Methods

Study Design and Sample Collection

This study was conducted prospectively in the Department of Obstetrics and Gynaecology, Shri Shankaracharya Institute of Medical Science, Bhilai, Chhattisgarh, in the Antenatal Care Clinic from June 2019 to November 2020 after ethical clearance from the institutional review board. Consecutive patients in different stages of pregnancy with or without symptoms of UTI attending the antenatal clinic were screened for significant bacteriuria. All the study subjects were first instructed to clean the area around the urethral meatus with soap and clean water and collect the urine with labia held apart. Fresh midstream urine was collected aseptically in sterile containers and submitted to the clinical microbiology laboratory.

All urine samples were examined microscopically for the presence of significant pyuria and grown in appropriate culture media. Significant pyuria was defined as ≥5 leukocytes per high power field in a centrifuged sample, or ≥10 leukocytes per mm^3 in a fresh uncentrifuged sample (10). Bacterial isolates were identified to species level & subjected to antibiotic susceptibility testing to a battery of antibiotic discs using the Kirby-Bauer disk diffusion method following the clinical laboratory standards institute (CLSI) 2013 guidelines(9).

Only urine culture-positive cases with significant colony count were included in the study. Colony count of $>10^5$ CFU/ml and >50,000 CFU/ml were considered significant for the midstream clean-catch sample and urethral catheterised sample respectively. For suprapubic samples, any numbers of pathogens were considered significant (10).

Urine culture showing no growth or Insignificant colony count and contaminated urine samples were excluded from the study.

The samples which were received were inoculated onto Blood Agar and Mac Conkey agar. After overnight aerobic incubation at 37°C, the plates showing significant growth as per the Kass count (single species count of more than 10^5 organisms per ml of urine) were processed further and the isolates were identified up to the species level by using standard biochemical tests.

Antibiotic sensitivity testing was done by the Kirby Bauer disc diffusion method according to the CLSI guidelines [5]. The following antibiotic discs (drug concentrations in µg) were used: Ampicillin (10), Amoxicillin/clavulanic acid (Augmentin 20/10), Gentamicin (10), Ceftazidime (30), Cefoperazone (75), Ceftriaxone (30), Cotrimoxazole (25), Ciprofloxacin (5), Amikacin (30), Norfloxacin (10), Nitrofurantoin (300), Imipenem (10) and Cefoxitin (30).

Screening of possible ESBL production was done using ceftriaxone (30 µg) and cefoperazone (75 µg). Those isolates with zone diameters less than 25 mm for ceftriaxone and less than 22 mm for cefoperazone were subsequently confirmed for ESBL production. Confirmation was done by Double Disk Synergy Test (DDST) as per CLSI guidelines. [6] Cefoperazone (75 µg) and Ceftazidime (30 µg) disks with and without Clavulanic acid (10 µg) were used. The organisms were phenotypically confirmed as ESBL producers only when they showed an increase in zone of inhibition greater than or equal to 5 mm when evaluated in combination with clavulanic acid. Quality control was performed testing *Escherichia coli* ATCC 25922.

Cefoxitin (30 µg) was used as a surrogate for oxacillin resistance. All strains of Staphylococcus aureus and coagulase-negative Staphylococcus resistant to cefoxitin were considered resistant to all the other beta-lactam antimicrobials including cephalosporins and carbapenems. [7]

Sample size: All patients were enrolled during the study period. None patient was excluded.

Statistical Analysis: Statistical analysis was done using the chi-square test and Student's t-test.

Results

During the 18-months study period, out of the 110 samples screened, a total of 66 (60%) samples of urine from pregnant females, in different stages of pregnancy were found to be positive on culture. The majority of the patients showing growth on culture had ASB (75%), while symptomatic UTI was present in only 25% of the pregnant females (*P*-value < 0.001). Most of the patients with symptomatic as well as asymptomatic UTI were in the first trimester of pregnancy (59%), followed by the third trimester (38%), only 3% had bacteriuria in the second trimester of pregnancy.

The Enterobacteriaceae accounted for nearly two-thirds of the isolates and E. coli alone accounted for 63% of the urinary isolates followed by Klebsiella pneumonia 8%. Among the Gram-positive cocci, CONS 9 (15%) were more frequently isolated than S. aureus (8.3%) [Table 1].

Table-1: Distribution of bacterial uropathogens isolated from pregnant women

Organism Isolated	No. of Isolates	%
E. coli	28	42.42
Klebsiella spp	3	4.54
Citrobacter	2	3.03
Acinetobacter	13	19.69
Enterococcus	17	25.75
Staph aureus	3	4.54
Total Positive urine culture	66	

Bacterial uropathogens isolated from pregnant women with UTI revealed the presence of high levels of single and multiple antimicrobial resistances against commonly prescribed drugs as shown in Table 2. Significantly high resistance was noted to the beta-lactam group of antimicrobials, fluoroquinolones and cotrimoxazole, both by the Gram-negative bacilli as well as Gram-positive cocci. Resistance was quite low against the piperacillin-tazobactam and Imipenem and virtually absent against nitrofurantoin.

Table-2: Resistance of bacterial uropathogens to antibiotics

Name of the Antibiotic	% Resistance
Ampicillin	65.9
Amoxycillin + Clavulanic acid	44
Gentamicin	68
Amikacin	56.75
Cotrimoxazole	77.5
Ciprofloxacin	84.48
Norfloxacin	72.72
Nitrofurantoin	0
Ceftazidime	79.31
Ceftriaxone	90.47
Piperacillin + Tazobactam	32.25
Imipenem	23.81

Discussion

Pregnancy is a unique state with anatomic and physiologic urinary tract changes. While ASB in non-pregnant women is generally benign, pregnant women with bacteriuria have an increased susceptibility to pyelonephritis. [8] Screening for and treatment of ASB in pregnancy has become a standard of obstetric care and most antenatal guidelines include routine screening for ASB. The present study was conducted to evaluate the prevalence of UTI in pregnant females and to review the drugs that can be used for the treatment of the same. Moreover, the data would also help the authorities to formulate antibiotic prescription policies. Proper investigation and prompt treatment are needed to prevent serious life-threatening condition and morbidity due to UTI that can occur in pregnant women. [1,2,8]

UTI may manifest as ASB or symptomatic bacteriuria. The prevalence of asymptomatic UTI has been previously reported to be 2- 13% in pregnant women compared with that of symptomatic UTI which occurs in 1-18% during pregnancy. [1,9-11] Our study findings also indicate that ASB was present in a fairly large percentage of pregnant females. We, therefore recommend screening of all pregnant women because timely intervention with the appropriate antibiotics can prevent drastic consequences. There is no consensus in the literature as to the optimal timing and screening frequency for ASB. Few recent studies suggest that urine should be cultured in each trimester of pregnancy to improve the detection rate. [12] Screening for and treatment of ASB to prevent pyelonephritis has also been shown to be cost-effective over a wide range of estimates according to earlier studies. [13]

Escherichia coli, an *Enterobacteriaceae*, is the major aerobic organism residing in the intestine and is the most commonly reported cause of UTI being a common faecal contaminant. Due to the short urethra of females and the closeness of the female anus and the vagina to the urethra, the organism is most likely to be inoculated into the urethra during the process of anal cleaning after defecation and during sexual intercourse. The predominance of *Escherichia coli* in cases of UTI is supported by our finding and that of other researchers.

It is also not surprising that *Staphylococcus aureus* is implicated in UTI in this study knowing that they are normal skin microbiota. They can be easily inoculated into the urethra from the surrounding skin during anal cleaning after defecation. The Gram-negative bacteria predominated, with *E. coli* being the most common pathogen (42.42%) isolated in the study. Other studies had also reported a similar frequency of UTI caused by *E. coli* [14,15].

Among the Gram-positive cocci, Enterococcus was isolated most frequently (25.75%), followed by *S. aureus* (4.54%), a view also corroborated by Rizvi *et al*.[16]There has been no systematic review of which antibiotic is best for the treatment of ASB. The antibiotic chosen should not only have a good maternal and fetal safety profile, but also excellent efficacy and low resistance rates in a given population. [17,18] Although many review articles suggest antibiotic regimens for both symptomatic and ASB in pregnancy, increasing antibiotic resistance complicates empirical regimens.

On antimicrobial susceptibility testing, it was noted that both the Gram-negative as well as Gram-positive isolates showed significantly high resistance to the beta-lactam group of antimicrobials which are considered the traditional drugs safe in pregnancy. Along with this the presence of ESBLs in 45% of the *E. coli* and 40% of the *Klebsiella* spp. isolates is a further cause of worry.

In a study from PGI Chandigarh on complicated UTIs, ESBL production was noted in a similar frequency. [19] Among the Gram-positive cocci more than one-third of the isolates were found to be methicillin-resistant. This is especially unfortunate because these isolates are then considered resistant to all the other currently available beta-lactam antimicrobials including cephalosporins and carbapenems.

Although the usage of beta-lactam antimicrobials is considered safe in pregnancy, the resistance to these drugs, by the common pathogens is alarmingly high as seen in our study which restricts their use to only the sensitive strains. There are similar reports of high-level resistance in the general population to these drugs by urinary pathogens. [15]

Fluoroquinolones have been shown to impair cartilage development in animal studies. Although this adverse effect has not been described in humans, quinolones should rather be avoided in pregnancy. As it is a high level of resistance to the tune of 85% resistance was noted in the current study. Other studies have also reported high resistance to the fluoroquinolones, to even the newer ones such as ofloxacin and pefloxacin. [15,20,21]

Aminoglycosides were found to have a better profile than another group of drugs but unfortunately these cannot be used in pregnant women. Similarly the carbapenems to which most of the isolates were found to be highly sensitive cannot be given in pregnancy. Regarding cotrimoxazole, concerns have been raised over the use in the first trimester due to association with neural tube and other birth defects. However, its use near term may lead to the displacement of bilirubin causing jaundice and kernicterus in the infant. [13,20] For this reason its use in pregnant women nearing term is also discouraged. Overall a high rate of resistance (77.5%) was seen among the urinary isolates in the current study. Similar discouraging results are also seen in another contemporary study. [13,15,21]

To conclude, we demonstrated a high level of resistance to the commonly used first-line agents like beta-lactams, fluoroquinolones and cotrimoxazole. As these oral agents usually achieve high urinary concentrations, it was initially thought that *in vitro* resistance may not result in treatment failure. However, recent studies have demonstrated otherwise. [17,22]

Nitrofurantoin has been used for more than five decades for the treatment of uncomplicated cystitis and it was found to remain active against most of the uropathogens. Recent data suggest that nitrofurantoin has retained a good amount of sensitivity (100%), both against ESBL producers and non-ESBL producers. [23,24] The absorption of oral nitrofurantoin is 40-50% and hence, it is enhanced when taken with food. The drug has minimal side effects and can be safely used for the treatment of uncomplicated cystitis even during pregnancy. [13,23]

The susceptibility patterns seen in our study seem to suggest that it is necessary to obtain sensitivity reports before initiation of antibiotic therapy in cases of suspected UTIs. High resistance rates to oral antibiotics in our study may be due to the uncontrolled consumption of these antibiotics in the community in the past decade. [25] On the other hand, resistance to amikacin, gentamicin and imipenem are low, likely reflecting lower usage of these drugs. Their safety in pregnancy is, however, questionable [13].

Various studies corroborate our findings suggesting nil resistance rates among uropathogens to nitrofurantoin.[13,23] This along with the fact that it is considered safe in all trimesters of pregnancy suggests that nitrofurantoin may be considered as a first-line agent for the treatment of UTIs among pregnant females.

Limitations

Hitherto, clinicians had relied on the information on drug detailing as given by drug companies' sales representatives for the treatment of UTI in the study centre and not on empirical evidence of susceptibility of the isolates. Also, epidemiological data on the microbial isolates in cases of UTI has been lacking. This study, therefore, provides first-hand information or documentation on both scientific evidence of microbial susceptibility of the isolates as well as the microbial etiology of UTI in the study centre.

This study is of international importance knowing that the world is a global village where people can migrate from one country to another with the attendant possibility of spreading resistant strains of microbes. A knowledge of the susceptibility profile as offered by this study will help clinicians offer objective treatment of UTI and so reduce the intercontinental spread of resistant microbial strain. However, the study did not provide the molecular bases of resistance to commercial antibiotics. It also did not establish the presence of extended beta-lactamase-producing isolates as a possible cause of resistance to the antibiotics.

What does this Study add?

The pattern of microorganisms and their sensitivity suggests that each unit should have the practice of microbial surveillance and antimicrobial stewardship. From this study, it has come out strongly that Nitrofurantoin is still the drug of choice for all community-acquired UTI and has retained its sensitivity for almost all gram-negative organisms.

Conclusion

In this study, *E. coli* and *Enterococcus* were the predominant pathogens. The bacterial isolates were resistant to the commonly prescribed drugs and so left the clinicians with only a few alternative drugs for UTIs treatment. The pattern of microbial resistance to antibiotics suggests that Ceftazidime, Fluoroquinolones, cotrimoxazole and Cefoxitin may not be the appropriate first-line agents in the empirical treatment of UTIs, instead; Nitrofurantoin may be considered. More studies on this topic will substantiate this finding.

What does the study add to the existing knowledge?

Routine surveillance and monitoring studies need to be constantly conducted to update clinicians on the prevalent pathogens and the rational and empirical treatment of UTIs. Aggressive and consistent health education using all possible social media is also recommended to combat the menace of drug resistance occasioned by inappropriate antibiotic use.

Contributions by authors

Monika Jindal: Conceptualised the study, developed the protocol, clinical examination and

Collection of data, and written the manuscript.

Shrikrishna Kumar Agrawal: Clinical examination and collection of data, and contributed to the manuscript.

Anju Pungale: Data Collection and data entry

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