

# Rising Prevalence of Antimicrobial Resistance in Urinary Tract Infections During Pregnancy: Necessity for Exploring Newer Treatment Options

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## ABSTRACT

**Background:** Urinary tract infections (UTI) are one of the most common medical complications of pregnancy. The emergence of drug resistance and particularly the Extended-spectrum beta-lactamase production by *Escherichia coli* and methicillin resistance in Staphylococci, limits the choice of antimicrobials.

**Materials and Methods:** Patients in different stages of pregnancy with or without symptoms of urinary tract infection attending the antenatal clinic of obstetrics and gynaecology were screened for significant bacteriuria, by standard loop method on 5% sheep blood agar and teepol lactose agar. Isolates were identified by using standard biochemical tests and antimicrobial susceptibility testing was done using Kirby Bauer disc diffusion method.

**Results:** A total of 4290 (51.2%) urine samples from pregnant females showed growth on culture. Prevalence of asymptomatic bacteriuria 3210 (74.8%) was higher than symptomatic UTI 1080 (25.2%). *Escherichia coli* was the most common pathogen accounting for 1800 (41.9%) of the urinary isolates. Among the gram-positive cocci, *coagulase* negative species of Staphylococci 270 (6.4%) were the most common pathogen. Significantly high resistance was shown by the gram negative bacilli as well as gram positive cocci to the  $\beta$ -lactam group of antimicrobials, fluoroquinolones and aminoglycosides. Most alarming was the presence of Extended-spectrum beta-lactamase in 846 (47%) isolates of *Escherichia coli* and 344 (36.9%) isolates of *Klebsiella pneumoniae*, along with the presence of methicillin resistance in 41% of *Staphylococcus* species and high-level aminoglycoside resistance in 45(30%) isolates of *Enterococcus* species. Glycopeptides and carbapenems were the only group of drugs to which all the strains of gram positive cocci and gram negative bacilli were uniformly sensitive, respectively.

**Conclusions:** Regular screening should be done for the presence of symptomatic or asymptomatic bacteriuria in pregnancy and specific guidelines should be issued for testing antimicrobial susceptibility with safe drugs in pregnant women so that these can be used for the treatment. For empirical treatment cefoperazone-sulbactam can be recommended, which is a safe drug, covering both gram positive and gram negative organisms and with a good sensitivity.

**Keywords:** Antimicrobial resistance, extended-spectrum beta-lactamase, high-level aminoglycoside resistance, MRSA, pregnancy, urinary tract infection

## INTRODUCTION

Urinary tract infections (UTIs) are one of the most common medical complications of pregnancy. Untreated upper UTI in pregnancy carries well documented risk of morbidity and rarely, mortality to the pregnant women.<sup>[1]</sup> Pregnancy causes numerous hormonal and mechanical changes in the body. Beginning in the sixth week, with peak incidence

during 22<sup>nd</sup> to 24<sup>th</sup> weeks, 90% of the pregnant females develop urethral dilatation increasing the risk of urinary stasis and vesicourethral reflux. In addition, glycosuria and aminoaciduria during pregnancy provide an excellent culture medium for bacteria in areas of urinary stasis.<sup>[2]</sup> These changes along with already short urethra and difficulty with hygiene due to the distended pregnant belly increase the frequency of UTI in pregnant females. Untreated bacteriuria in pregnancy either asymptomatic or symptomatic is associated with a 50% increase in the risk of low birth weight and a significant increase in the risk of premature delivery,<sup>[3]</sup> pre-eclampsia,<sup>[4]</sup> hypertension, anemia,<sup>[5]</sup> and postpartum endometritis.<sup>[6]</sup>

A limited and predictable spectrum of organisms

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causes UTI in pregnant otherwise healthy females. *Escherichia coli* is the primary urinary tract pathogen accounting for 75%--90% of uncomplicated UTI isolates. Other uropathogens include *Staphylococcus saprophyticus* in 5%--10% episodes and *Klebsiella pneumoniae*, *Proteus mirabilis* and group B *Streptococci* in less than 5%.<sup>[7]</sup> Because of altered pharmacokinetics, drug use in pregnancy may have unpredictable effects. Certain antibiotics are unsuitable for use due to their potential toxicity.<sup>[8,9]</sup> Antimicrobial agents considered safe in pregnancy are nitrofurantoin,  $\beta$  lactam antibiotics including both penicillins and cephalosporins and fosfomycin trometamol.<sup>[10]</sup> However, the emergence of drug resistance and particularly the ESBL production by *Escherichia coli* and methicillin resistance in *Staphylococcus species*, limits the choice of antimicrobials. This prospective study was designed to find out the prevalence of various organisms in UTI among the pregnant females and their antimicrobial resistance pattern and to review the drugs that can be used for the treatment of the same.

## MATERIALS AND METHODS

The study was conducted prospectively in the Department of Microbiology, Jawaharlal Nehru Medical College and Hospital, AMU Aligarh from June 2002 to June 2007. Consecutive patients in different stages of pregnancy with or without symptoms of urinary tract infection attending the antenatal clinic of Obstetrics and Gynaecology were screened for significant bacteriuria, by standard loop method on 5% sheep blood agar and teepol lactose agar. Significant bacteriuria is defined as two consecutive positive cultures of  $>10^5$ cfu/ml of midstream urine with growth of the same species.<sup>[8,11]</sup> For pregnant women with symptoms, a diagnostic criterion of  $>10^3$  organisms/ml of midstream urine in a single culture was taken as significant bacteriuria.<sup>[9,11]</sup> Non-pregnant females and those on antimicrobial therapy for UTI or for any other illness were excluded from the study. Inadequate urine samples (less than 10 ml urine), urine bag collected specimens, specimens collected more than 2 h before, specimens submitted in leaking or dirty unsterile containers and specimens revealing growth of more than two types of bacteria on culture were also excluded from the study.

Isolates in significant numbers were identified by using standard biochemical tests.<sup>[12]</sup> Antimicrobial susceptibility testing was done for all the isolates using Kirby Bauer disc diffusion method as recommended by CLSI M2-A9.<sup>[13]</sup> The antibiotic panels for each group of isolates were selected according to the CLSI guidelines M100-S16<sup>[14]</sup>

were obtained from HiMedia, India. The antimicrobials tested for the gram negative bacteria were amikacin (30  $\mu$ g), gatifloxacin (5  $\mu$ g), ofloxacin (5  $\mu$ g), gentamicin (10  $\mu$ g), ciprofloxacin (5  $\mu$ g), ceftazidime-sulbactam (75/75  $\mu$ g), and nitrofurantoin (300  $\mu$ g). Screening of possible ESBL production was done by using ceftazidime (30  $\mu$ g) and ceftazidime-sulbactam (75  $\mu$ g). Those isolates with zone diameters less than 25 mm for ceftazidime and less than 22 mm for ceftazidime-sulbactam were subsequently confirmed for ESBL production. Confirmation was done by noting the potentiation of the activity of ceftazidime in the presence of ceftazidime sulbactam. Induction of AmpC synthesis was based on the disc approximation assay using imipenem as inducer.<sup>[15]</sup> Detection of MBL was done by Hodge test and Double Disc synergy test using EDTA. The method was as described by Lee *et al.*<sup>[16]</sup>

Among the gram positive cocci the antimicrobials tested for *Staphylococcal* species were oxacillin (1  $\mu$ g), amoxicillin (30  $\mu$ g), gentamicin (10  $\mu$ g), ampicillin (10  $\mu$ g), clindamycin (2  $\mu$ g), and vancomycin (30  $\mu$ g). For streptococcus species the antimicrobials tested were amoxicillin (30  $\mu$ g), gentamicin (10  $\mu$ g), erythromycin (15  $\mu$ g), high content gentamicin (120  $\mu$ g), high content streptomycin (300  $\mu$ g), and vancomycin (30  $\mu$ g). Oxacillin (1 $\mu$ g) for the detection of Methicillin-resistant *S. aureus* (MRSA) and 120  $\mu$ g gentamicin and 300  $\mu$ g streptomycin disc for detection of high level resistance to aminoglycosides (HLAR) in *Enterococci*.<sup>[17]</sup>

## Statistical analysis

Statistical analysis was done using chi-square test and Student's *t*-test.

## RESULTS

During the five-year study period, a total of 8379 urine samples of pregnant females were collected out of which 4290 (51.2%) showed growth on culture. Majority of the patients showing growth on culture had asymptomatic bacteriuria 3210 (74.8%), while symptomatic UTI was present in only 1080 (25.2%) of the pregnant females (*P* value < 0.001, CI 95% and the degree of freedom is 1). Most of the patients with symptomatic UTI complained of increased frequency and burning during micturition along with urgency. Fever was present in just a limited number of patients. Most of the patients with symptomatic as well as asymptomatic UTI were in the first trimester of pregnancy 2296 (53.5%), followed by third trimester 1909 (44.5%), and only 85 (1.98%) had bacteriuria in the second trimester of pregnancy.

## Microbiology

The Enterobacteriaceae accounted for nearly two-third of the isolates 3315 (77.3%) and *Escherichia coli* alone accounted for 1800 (41.9%) of the urinary isolates, followed by *Klebsiella pneumoniae* 930 (21.7%), *Citrobacter species* 315 (7.3%) [*C. koseri* 298(94.6%) isolates, *C. amalonaticus* 10 (3.2%), *C. freundii* 7 (2.2%)] and *Proteus mirabilis* and *Proteus vulgaris* together accounting for 270 (6.3%) isolates. In 150 (3.4%) urinary specimens *Pseudomonas aeruginosa* and other *Pseudomonas species* were isolated. Among the gram positive cocci, Coagulase negative Staphylococci were the predominant isolate accounting for 270 (6.4%) of the cases of UTI. On novobiocin sensitivity testing 74.1% (200) of the coagulase negative isolates were *Staphylococcus saprophyticus* and 25.9% (70) isolates were *Staphylococcus epidermidis*. *S. aureus* 255(5.94%), *Enterococcus faecalis* 150 (3.5%), and *Streptococcus species* 150 (3.5%) were the other common gram positive organisms causing UTI in pregnant females [Table 1].

### Antimicrobial resistance

The resistance rates among the gram negative and gram positive isolates are given in Tables 2 and 3, respectively.

### Penicillins and cephalosporins

A significantly high resistance was noted to the  $\beta$ -lactam group of antimicrobials both by the gram negative bacilli as well as the gram positive cocci. Nearly half of the isolates of the Enterobacteriaceae, i.e., 1698 (51.2%) and 96 (64.3%) of the *Pseudomonas* isolates were resistant to cefotaxime, a third generation cephalosporin. However, cefoperazone-sulbactam (a combination of third generation cephalosporin with  $\beta$  lactamase inhibitor) was found to be a better drug with sensitivity of around 90% (3056) isolate of Enterobacteriaceae and 86% (128) of *Pseudomonas* isolates. 846 (47%) isolates of *Escherichia coli* and 344 (36.9%) isolates of *Klebsiella pneumoniae* were found to be ESBL producers. 331 (10%) of the isolates of Enterobacteriaceae were found to be Amp C producers. However, none of the isolates were found to produce metallo- $\beta$ -lactamases. Amongst the gram positive cocci, 92 (34%) isolates of Coagulase negative *Staphylococcus species* and 87 (34.1%) *Staphylococcus aureus* (MRSA) isolates were resistant to oxacillin. All the strains of *Staphylococcus species* resistant to oxacillin were considered resistant to all the other  $\beta$ -lactam antimicrobials including cephalosporins and carbapenems. Significantly low resistance was noted for amoxicillin 15 (10%) by the *Enterococcus faecalis*.

**Table 1: Distribution of various pathogens causing UTI in pregnant females**

Organism	Prevalance no. (%)
<i>Escherichia coli</i>	1800 (41.9)
<i>Klebsiella pneumoniae</i>	930 (21.7)
<i>Citrobacter koseri</i> and <i>C. amalonaticus</i> , <i>C. freundii</i>	315 (7.34)
<i>Proteus mirabilis</i> and <i>P. vulgaris</i>	270 (6.29)
<i>Pseudomonas species</i>	150 (3.4)
<i>Staphylococcus saprophyticus</i> and <i>S. epidermidis</i>	270 (6.4)
<i>Staphylococcus aureus</i>	255 (5.9)
<i>Enterococcus faecalis</i>	150 (3.4)
<i>Streptococcus species</i>	150 (3.4)
Total	4290 (100)

### Fluoroquinolones

Fluoroquinolones had a poor activity against the Enterobacteriaceae as well as on other gram negative and also on gram positive isolates. Gatifloxacin was better than the other fluoroquinolones, with 2066 (62.3%) of the Enterobacteriaceae isolates and 106 (69.8%) of the *Pseudomonas* isolates showing resistance. Around two-third isolates of *S. aureus* 189 (74.1%) and of Coagulase negative *Staphylococcus species* 197 (72.9%) were resistant to gatifloxacin.

### Nitrofurantoin

It was found have a good sensitivity profile with just 1326 (40%) Enterobacteriaceae, and 94 (36.8%) *S. aureus* and 91 (33.7%) isolates of CONS showing resistance to the same.

### Aminoglycosides

Amikacin had a better spectrum of antimicrobial sensitivity, with resistance to just 630 (19%) of the isolates of Enterobacteriaceae and 54 (35.8%) of the *Pseudomonas* isolates. However, the resistance to aminoglycosides was higher among the gram positive cocci 151(59.2%) in *Staphylococcus aureus* and 162 (60%) in CONS. On testing with high content gentamycin and high content streptomycin 45 (30%) of *Enterococcus faecalis* were found to have high-level aminoglycoside resistance (HLAR).

### Carbapenems and glycopeptides

All the gram negative and all the gram positive isolates were uniformly sensitive to carbapenems and glycopeptides, respectively.

## DISCUSSION

The study was conducted to evaluate the prevalence of UTI in pregnant females and to review the drugs that can

**Table 2: Antimicrobial susceptibility pattern of gram negative organisms isolated from urine**

Antimicrobials tested	Enterobacteriaceae n = 3315		Pseudomonas species n = 150	
	Sensitive no. (%)	Resistant no. (%)	Sensitive no. (%)	Resistant no. (%)
Amikacin	2658 (81.1)	630 (19)	96 (64.2)	54 (35.8)
Cefotaxime	1617 (48.8)	1698 (51.2)	54 (35.7)	96 (64.3)
Cefoperazone-sulbactam	3056 (92.2)	259 (7.8)	128 (85.7)	22 (14.3)
Ciprofloxacin	1176 (35.5)	2139 (64.5)	22 (14.2)	128 (85.8)
Gatifloxacin	1249 (37.7)	2066 (62.3)	44 (30.2)	106 (69.8)
Gentamycin	2134 (64.4)	1181 (35.6)	64 (42.8)	86 (57.2)
Imipenem	3315 (100)	00 (00)	150 (100)	00 (00)
Ofloxacin	828 (25)	2487 (75)	30 (20)	120 (80)
Nitrofurantoin	1989 (60)	1326 (40)	-	-

**Table 3: Antimicrobial susceptibility pattern of gram positive cocci isolated from urine**

Antimicrobials tested	<i>Staphylococcus aureus</i> n = 255		<i>Staphylococcus saprophyticus</i> n = 200		<i>Staphylococcus epidermidis</i>		<i>Enterococcus faecalis</i> n = 150	
	Sensitive no.(%)	Resistant no.(%)	Sensitive no.(%)	Resistant no.(%)	Sensitive no.(%)	Resistant no.(%)	Sensitive no.(%)	Resistant no.(%)
Amoxicillin	-	-	-	-	-	-	135 (90)	15 (10)
Oxacillin	168 (65.9)	87 (34.1)	132 (66)	68 (34)	46 (65.7)	24 (34.3)	-	-
Erythromycin	120 (47)	135 (53)	58 (29)	142 (71)	13 (18.6)	57 (81.4)	90 (60)	60 (40)
Gatifloxacin	66 (26)	189 (74)	59 (29.5)	41 (70.5)	14 (20)	56 (80)	-	-
Gentamicin	164 (41)	151 (59)	85 (42.5)	115 (57.5)	23 (32.9)	40 (57.1)	-	-
High content gentamicin	-	-	-	-	-	-	105 (70)	45 (30)
High content streptomycin	-	-	-	-	-	-	105 (70)	45 (30)
Vancomycin	255 (100)	00 (00)	200 (100)	00 (00)	70 (100)	00 (00)	150 (100)	00 (00)

be used for the treatment of the same. During the five-year study period, a total of 4290 samples of urine from pregnant females, in different stages of pregnancy were found to be positive on culture. The prevalence of asymptomatic bacteriuria was higher (nearly two-third of the total; 74.8%) than symptomatic UTI (25.2%). Females in the first and third trimester of pregnancy had greater incidence of asymptomatic as well as symptomatic bacteriuria.

The gram negative bacteria predominated, with *Escherichia coli* being the most common pathogen (41.9%) isolated in the study. Other studies had also reported a similar frequency of UTI caused by *Escherichia coli*.<sup>[18,19]</sup> Amongst the gram positive cocci, *CONS* were isolated most frequently (6.4%), followed by *Staphylococcus aureus* (5.9%), *Enterococcus faecalis* (3.5%), and *Streptococcus* species (3.5%). However, other authors have reported *S. aureus* as the most common urinary pathogen among the gram positive cocci followed by other *Staphylococcus* species.<sup>[18]</sup>

On antimicrobial susceptibility testing, it was noted that both the gram negative bacilli as well as the gram positive cocci showed a significantly high resistance to the  $\beta$ -lactam group of antimicrobials which are considered the traditional drugs safe in pregnancy. There are similar reports of high level resistance in the general population to these drugs by the urinary pathogens.<sup>[19]</sup> Along with this the presence of extended spectrum- $\beta$ -lactamases in about half

of *E. coli* isolates and around 37% of *Klebsiella* was noted, which is a cause for worry. In a study from PGI Chandigarh on complicated UTI, ESBL production was noted in a similar frequency.<sup>[20]</sup> Among the gram positive cocci, nearly one-third isolates of *S. aureus* and Coagulase negative *Staphylococcus* species were found to be methicillin resistant. This is an alarming finding, since these isolates should be considered resistant to all the other currently available  $\beta$ -lactam antimicrobials including cephalosporins and carbapenems.<sup>[21]</sup> Moreover, the methicillin resistant strains of *Staphylococci* are found to be multidrug resistant<sup>[22]</sup> as reported by other studies. This further restricts the treatment options. Although the usage of  $\beta$  lactam antimicrobials is considered safe in pregnancy, but the resistance to these drugs, by the common pathogens is alarmingly very high as seen in our study which restricts their use to only the sensitive strains.

Among the fluoroquinolones least resistance was exhibited to gatifloxacin, but still it was as high as 62%. Other studies have also reported high resistance to fluoroquinolones, to even the newer ones such as ofloxacin and pefloxacin.<sup>[19]</sup> This may be due to the overuse of these drugs. Second, fluoroquinolones are not considered safe in pregnancy.<sup>[23]</sup> Nitrofurantoin, a urinary antiseptic, was found to have a better susceptibility. Though considered safe by some authors,<sup>[24,25]</sup> nitrofurantoin had been reported to increase the risk of haemolysis and glucose-6-phosphate

dehydrogenase (G6PD) deficiency in the neonates.<sup>[8,26]</sup> Aminoglycosides were found to have a better profile than other group of drugs but unfortunately these cannot be used in pregnant women. Similarly the carbapenems and glycopeptides to which all the strains of the gram negative bacilli and gram positive cocci, respectively, were found to be uniformly sensitive cannot be given in pregnancy.

The problem of selecting antibacterial treatment in pregnancy, is besides the cost benefit, the possible conflict between choosing a well-established drug that is well tolerated and empirically known to be harmless to the mother and the fetus, and choosing a drug to which there is a low level of bacterial resistance.

The drugs other than the  $\beta$ -lactams and nitrofurantoin, which are considered safe for the treatment of UTI in pregnant females are cotrimoxazole, fosfomycin trometamol and pivmecillinam.

Fosfomycin trometamol had been reported to have high activity against the majority of Enterobacteriaceae, but not toward the gram positive bacteria.<sup>[11,12]</sup> The lack of teratogenicity in animals and apparently safe use of fosfomycin during human pregnancy indicate that the drug presents a low risk, if any, to the fetus. Because the number of first trimester human exposures is limited, however, treatment would be best delayed until after the period of organogenesis.<sup>[27]</sup>

Cotrimoxazole (a combination of sulfamethoxazole and trimethoprim in a ratio of 5:1 or 1:2) can be used for the treatment of UTI in pregnant women if its benefits are deemed to outweigh the potential risks. Use of cotrimoxazole during pregnancy may have beneficial consequences for infants, reducing rates of low birth weight, preterm delivery and neonatal mortality. However, its use near term may lead to the displacement of bilirubin causing jaundice and kernicterus in the infant.<sup>[28,29]</sup> For this reason, cotrimoxazole should not be used near term in pregnant women.

Pivmecillinam, which is a prodrug of mecillinam a  $\beta$ -lactam antibiotic with a novel site of action and with specific and high activity against the gram negative organisms especially *Escherichia coli* and other Enterobacteriaceae. The level of resistance to this drug has remained on a low level (<2% in *E. coli*) and its safety in pregnancy had been confirmed by clinical studies on pregnant women with UTI.<sup>[30]</sup> Pivmecillinam is thus, an appropriate agent for use in empirical treatment of acute uncomplicated UTI in pregnancy.

The study highlights the fact, regular screening should be done for the presence of symptomatic or asymptomatic bacteriuria in pregnancy and specific guidelines should be issued for testing antimicrobial susceptibility with safe drugs in pregnant women so that these can be used for the treatment, since with the emergence of drug resistance amongst the gram positive and gram negative bacteria, the choice of drugs for the treatment of UTI is very limited. Moreover, in most of the microbiology laboratories, no specific drugs are used for the antimicrobial susceptibility testing of the urinary isolates from the pregnant females. This further shrinks the spectrum of drugs, since most of the antimicrobials which can be given in otherwise healthy individuals, may not be safe in pregnancy. However, when empirical treatment is to be started before the culture and sensitivity report can be ensured, than we suggest the use of cefoperazone-sulbactam because it is a relatively cheap drug, which safe in pregnancy, covers both the gram negative bacilli and the gram positive cocci, and as seen in our study is found to have a good sensitivity profile. We suggest that periodic surveys should be done for the prevalence and susceptibility pattern of the common pathogens causing UTI in local regions especially keeping the pregnant females as the target group.

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