

Original Article

# Profile of uropathogens in pregnancy over 5 years from a large tertiary center in South India

Liji Sarah David<sup>1</sup>, N. D. Varunashree<sup>1</sup>, Emily Divya Ebenezer<sup>1</sup>, Preethi Raja Navaneethan<sup>1</sup>, Richa Sasmita Tirkey<sup>1</sup>, Swati Rathore<sup>1</sup>, Gowri Mahasampath<sup>2</sup>, Thambu David<sup>3</sup>, Jiji Elizabeth Mathews<sup>1</sup>, Rani Diana Sahni<sup>4</sup>

Departments of <sup>1</sup>Obstetrics and Gynecology, <sup>2</sup>Bio-Statistics, <sup>3</sup>Medicine, <sup>4</sup>Microbiology, Christian Medical College, Vellore, Tamil Nadu, India.

## ABSTRACT

**Objectives:** Urinary tract infections (UTIs) are a common medical problem in both antenatal and postnatal women. Data from India on the demography of these women, microbiology and antimicrobial susceptibility of the causative bacteria, need elucidation.

**Material and Methods:** We performed an observation study that collected data on UTI in antenatal and postnatal women between 2013 and 2017 at our tertiary care center in South India. Antenatally, urine dipstick-positive patients, high-risk, and symptomatic patients submitted urine cultures. Postnatally, all symptomatic patients had urine cultures. This was 20% of all antenatal and postnatal women resulting in 20,203 cultures.

**Results:** Of 20,203 cultures, significant bacteriuria was seen in 9.48% of antenatal and 13.28% of postnatal women. A higher mean age was seen among those with UTI, antenatal 27 (SD 3.5) and postnatal 26.4 (SD 4.7) years versus 23.9 (SD 3.6) with no growth in culture. The mean BMI among antenatal was 28.2 (SD 3.5) and postnatal was 28 (SD 7.4). Most (60%) were primigravida. At delivery, 37% required cesarean sections while 21.2% required instrumental delivery. Recurrent UTI was seen in 25% antenatally and 10% in the postnatal period. *Escherichia coli* accounted for 66 and 60% of infections among antenatal and postnatal women, respectively. *Enterococcus* species accounted for 13% in both while *Klebsiella* species was 4.9 and 7.3%, respectively. Among *E. coli*, 68.3 and 59.2% of isolates in antenatal and postnatal period were cefpodoxime susceptible. Nearly 75% of ante- and postnatal isolates were susceptible to amoxicillin-clavulanate while 90.2% and 92.5% were susceptible to nitrofurantoin. *Enterococci* spp. up to 84.4 and 97.1% in ante- and postnatal isolates were susceptible to ampicillin, 64.4 and 77.4% susceptible to high-level gentamicin, and 84 and 95.5% susceptible to nitrofurantoin. Asymptomatic bacteriuria in pregnancy was documented in 2.1% of antenatal outpatients and *E. coli* was isolated in 74% of these cultures.

**Conclusion:** Importance of microbiological evidence prior to administration of antimicrobials is evidenced by 79% negative cultures in this 5-year cohort. *Escherichia coli* accounted for 60-66% of significant bacteriuria followed by *Enterococcus* and *Klebsiella* species with 30-40% *E.coli* probable ESBL producers. Nitrofurantoin followed by amoxicillin-clavulanate were found to be the best oral antimicrobial options.

**Keywords:** Urinary tract infections, Asymptomatic bacteriuria, Pregnancy, Uropathogens

## INTRODUCTION

Urinary tract infection (UTI) is usually seen as asymptomatic bacteriuria and is present in 8–10% of antenatal women.<sup>[1]</sup> About 1.5–3% of postnatal women have UTI depending on the mode of delivery, with UTI being more common after cesarean delivery.<sup>[2]</sup> It is known from studies that 30% of antenatal women with asymptomatic bacteriuria develop pyelonephritis. Moreover, the association of UTI and preterm birth<sup>[3]</sup> and the consequent economic strain makes it an important entity for screening in pregnancy. Small studies from the west have described the profile of microorganisms in UTI complicating pregnancy<sup>[4-8]</sup> and there are similar

small studies from India.<sup>[9,10]</sup> Antibacterial resistance has always been an area of concern with extended spectrum beta-lactamase (ESBL)-producing strains increasing in number, especially in India.<sup>[11-14]</sup> Thus, the aim of our study was to assess the prevalence of significant UTI in pregnancy and to study the microbiologic profile and antibiotic sensitivity trend of these infections over 5 years in a large tertiary center.

## MATERIAL AND METHODS

This retrospective study was done over 5 years, between 2013 and 2017 after the Institutional Review Board Clearance (Retro 11336 dated April 18, 2018, and IRB.No.11758 dated

\*Corresponding author: Richa Sasmita Tirkey, MS, DGO, Assistant Professor, Department of Obstetrics and Gynecology, Christian Medical College, Ida Scudder Road, Vellore, Tamil Nadu, India. coronistrial@yahoo.co.in

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December 19, 2018). Our tertiary center in South India had more than 100,000 antenatal outpatients (OP) and around 13,000 booked deliveries per annum. During this period, spontaneous preterm labor was seen in 8% of antenatal women. The information on urine culture during this period was obtained from the microbiology laboratory data records and the hospital electronic medical record database.

The policy in the antenatal clinic was to screen for UTI using the urine dipstick method. Urine cultures were sent only if the screening test was positive, if the woman had significant urinary symptoms, if there was history of previous preterm delivery or a bad obstetric outcome, and if there was threatened preterm labor in the current pregnancy. Postnatally, urine culture was sent for woman with fever, urinary symptoms such as dysuria, and significant retention of urine. About 20% of antenatal and postnatal women had urine cultures done. A colony count of more than  $10^5$  colony-forming units (CFU)/mL was considered as significant bacteriuria and  $10^3$ – $10^5$ /mL was taken as probably significant culture. Less than  $10^3$  CFU/mL was taken as a negative culture.

Recurrence of UTI was defined as two or more occurrences within 6 months.<sup>[15]</sup>

Urine specimens received were processed within 1 h by the semi-quantitative culture method.<sup>[16]</sup> Gram stain was performed as an initial assessment of the uncentrifuged urine specimen to grade the presence of inflammatory reactive cells, epithelial cells, and bacteria and to determine the quality of the specimen.<sup>[17-19]</sup> Those found to be smear negative were processed by the automated culture method (HB and L Alifax, Italy) with a limit of detection of 350 CFU/ml. The routine semi-quantitative culture was performed with 10  $\mu$ l of the specimen on the sterile and quality passed 7% sheep blood agar and MacConkey media, prepared in the department of clinical microbiology.<sup>[16,18]</sup> The cultures were incubated aerobically at 37°C for up to 48 h.

Culture interpretation was done using the following criteria:

1. Amount of inflammatory response as seen on Gram-stained smears of the urine specimen.
2. The concomitant symptoms at the time of culture
3. The growth in culture.

Culture growth up to two organisms with  $>100,000$  CFU/mL was interpreted as significant bacteriuria.<sup>[15,17,18,20]</sup> Colony counts of 1000–100,000 CFU/ml up to two organisms were interpreted as probably significant bacteriuria. The presence of more than two pathogens in counts more than 1000 CFU/mL and normal urethral flora was considered as a mixture of organisms and contaminants, respectively, while colony counts of  $<1000$  CFU/mL of a single organism were reported as insignificant bacteriuria.

The Gram-negative bacilli were identified using the oxidase test and the preliminary screening media consisting of the mannitol motility media, triple sugar iron agar, peptone water, Simmons citrate, and Christensen's urea media and characterized further to derive a species identification. *Enterococcus* species was identified using bile esculin agar.

Susceptibility testing was performed by the Kirby–Bauer disk diffusion method on Mueller-Hinton agar, Difco, India, in accordance with the Clinical Laboratories Standard Institute guidelines relevant for each year.<sup>[21]</sup> Standard American Type Culture Collection control strains were used as quality control strains for the drugs tested. The drugs included in the panels for testing were based on the bioavailability in the urinary tract, the prevalence of resistance, and the spectrum of action. *Enterobacterales* were tested against, first-line agents cefpodoxime (10  $\mu$ g), nitrofurantoin (300  $\mu$ g), cotrimoxazole (1.25/23.75  $\mu$ g), ciprofloxacin (5  $\mu$ g), gentamicin (10  $\mu$ g), and amoxicillin-clavulanate (20/10  $\mu$ g) and if resistant to the first-line against, they were test against amikacin (30  $\mu$ g), piperacillin-tazobactam (100/10  $\mu$ g), and meropenem (10  $\mu$ g). Cefpodoxime resistance was a marker of possible ESBL-producing bacteria.

The non-fermenting Gram-negative bacilli were tested against ceftazidime (30  $\mu$ g), levofloxacin (5  $\mu$ g), amikacin (30  $\mu$ g), piperacillin-tazobactam (100/10  $\mu$ g), and meropenem (10  $\mu$ g).

*Enterococcus* species were tested against first-line agents such as ampicillin (10  $\mu$ g), nitrofurantoin (300  $\mu$ g), high-level gentamicin (120  $\mu$ g) plus vancomycin (30  $\mu$ g), teicoplanin (30  $\mu$ g), and linezolid (30  $\mu$ g). If these species were resistant to the first line agents or for *Staphylococcus* species the susceptibility to cefoxitin (30  $\mu$ g) and nitrofurantoin (300  $\mu$ g) were also determined.

Data were summarized using mean standard deviation for continuous variables and frequency along with percentage for categorical variables.

## RESULTS

A total of 20,203 urine specimens for culture were sent from the OP and inpatients of the obstetrics department from 2013 to 2017 [Table 1]. The OP specimens were mostly antenatal and the inpatient (IP) specimens were mostly postnatal. Among the OP specimens, 9.49% (1021/10755) had significant organisms on culture while 13.58% (1283/9448) were significant among IP specimens [Figure 1]. Among the total urine cultures sent, 9448 were postnatal samples and 10,755 antenatal samples. Of the antenatal samples, the approximate incidence of significant UTI was 1.57% (1021/64,933) and 2% (1283/64,933) in postnatal samples.

Among 10,755 antenatal urine cultures, 1027 were probably significant, 50 were improperly collected or mixture of organism, and 9627 had no growth. Among the 9448

**Table 1:** Overview of obstetric department urine culture ordering frequency in a large tertiary center.

Year	Booked births	Total number urine cultures	Outpatient	Antenatal urine cultures positive	Hospitalized patients	Postnatal urine culture positive
2013	11,948	4345	2677	180	1668	225
2014	12,642	3915	2225	205	1690	181
2015	13,399	3840	1980	209	1860	244
2016	13,462	4289	2140	256	2149	307
2017	13,482	3814	1733	171	2081	326
Total	64,933	20,203	10,755	1021	9448	1283

postnatal samples, 879 had probably significant growth, 2214 had improperly collected or mixture of organism, and 5072 samples had no growth. Among the postnatal samples that were significant, 35% had delivered normally and 65% by operative delivery. The demographic features of women with positive cultures compared to baseline characteristics of the birth cohort are recorded in [Table 2]. The number of patients presenting with significant UTI rose steadily between 4 and 40 weeks among the antenatal patients with its frequency, being highest during the third trimester. Postnatally, the majority of significant bacteriuria cases were seen at 1 week postpartum with 90.9% occurring in hospital [Figure 2a and b].

Recurrent significant UTI was seen in 25% of women in the antenatal period and 10% of women in the postnatal period.

### Uropathogens

The spectrum of microorganisms causing significant bacteriuria is described in [Figure 3]. *Escherichia coli* accounted for 66 and 60% of infections among antenatal and postnatal women, respectively. *Enterococcus* species accounted for 13% in both while *Klebsiella* species was 4.9 and 7.3%, respectively.

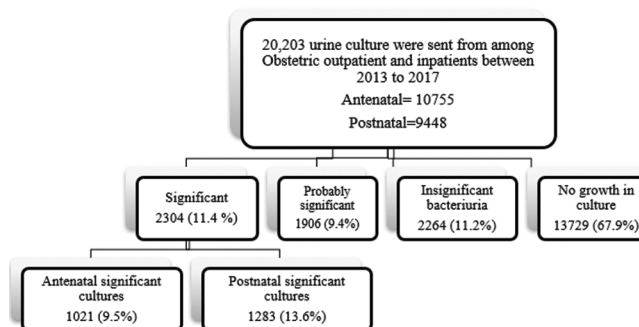
*E. coli* sensitivity [Table 3] suggests that overall 68.3 and 59.2% of isolates in antenatal and postnatal period were cefpodoxime susceptible. Nearly 75% of ante- and postnatal isolates were susceptible to amoxicillin-clavulanate. Susceptibility to oral agent nitrofurantoin in *E. coli* isolated among antenatal and postnatal cultures was seen in 90.2% and 92.5%, respectively. Among *Enterococci* species, susceptibility to ampicillin was seen in 84.4 and 97.1% of isolates in ante- and postnatal samples while susceptibility to high-level gentamicin was present in 64.4 and 77.4%, respectively. This susceptibility pattern remained the same in 5-year period with no significant change.

### DISCUSSION

This data of UTI from 64,933 births can give us important information that will be useful to tailor screening and treatment of UTI in pregnancy in this geographic region.

**Table 2:** Basic baseline patient characteristics of patients with significant bacteriuria in culture.

Patient characteristics	Total number of positive results (2013–2017) 2304	Total birth (2013–2017) 64,933
Age in years, Mean and SD	27 (SD=14.45)	29.42%
BMI, Kg/m <sup>2</sup>	28 (SD=5.1)	25.84%
Parity Primigravida, %	1318 (56.4%)	50%
Medical complications, %	1317 (56.4%)	11.13%
Obstetric complications, %	1704 (73%)	56.57%

**Figure 1:** Study flow diagram.

Only 11.4% (2304/20,203) of all cultures that were sent during this period in pregnancy were positive. Approximately 9% of antenatal cultures were positive in a setting where cultures were not done universally but as the second step following a primary screening protocol. Postnatal cultures that were sent only for symptomatic women were positive in 13.7% of samples. This was common in the 1<sup>st</sup>–2<sup>nd</sup> week following delivery as seen in other studies.<sup>[2,22]</sup> Overall incidence of 1–2% that was seen in this study<sup>[1,2,4]</sup> was similar to other studies.

This study has also been able to find recurrence rates of infection both antenatally and postnatally. UTI with both instrumental delivery and cesarean delivery was more common than with normal delivery, and this could be mainly due the increased catheterization associated with operative deliveries as seen in another study.<sup>[23]</sup> Optimization of collected urine samples has been a challenge especially when collected from postnatal women. This study has shown

**Table 3:** Cumulative antimicrobial susceptibility pattern of pathogens causing significant bacteriuria.

	Antenatal	Sensitivity (%)	Postnatal	Sensitivity (%)
<b>3A <i>Escherichia coli</i> (n=1384)</b>				
Nitrofurantoin	547	90.2	679	92.5
Cotrimoxazole	386	64.5	447	60.3
Ciprofloxacin	369	62.1	48	16
Cefpodoxime	398	68.3	441	59.2
Amoxicillin-clavulanate	645	79.3	556	73.9
Piperacillin-tazobactam	28	77.7	97	84.2
Cefoperazone-sulbactam	42	89.3	103	91.1
Gentamicin	509	83	603	80.4
Netilmicin	36	97.2	109	94.7
Amikacin	47	95.9	110	94.8
Imipenem	35	97.2	112	97.3
Meropenem	37	97.3	112	97.3
<b>3B <i>Enterococcus species</i> (n=330)</b>				
Ampicillin	98	84.4	172	97.1
Nitrofurantoin	95	84	168	95.4
High-level gentamicin	76	64.4	137	77.4
Teicoplanin	5	100	4	100
Linezolid	5	100	4	100
Vancomycin	5	100	2	100
<b>3C <i>Klebsiella species</i> (n=318)</b>				
Nitrofurantoin	133	6	149	5
Cotrimoxazole	139	84.2	135	97
Ciprofloxacin	139	92.8	164	80
Cefpodoxime	139	84.2	165	66.7
Amoxicillin-clavulanate	139	84.2	165	69
Piperacillin-tazobactam	10	50	26	65.4
Cefoperazone-sulbactam	13	80	31	64.5
Gentamicin	60	92.8	165	81.2
Netilmicin	8	70	26	69.2
Amikacin	13	80	31	71
Imipenem	8	70	26	80.8
Meropenem	8	70	26	80.8

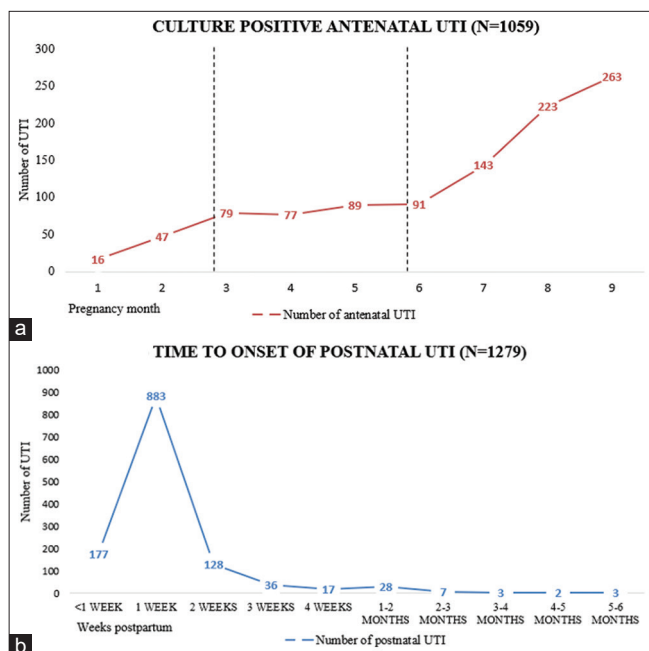
properly collected samples in 90% of antenatal women and 70% postnatal women.

*E. coli* known to be the most common uropathogen universally in UTI for both postnatal and antenatal women was seen in 60% of the samples. *Enterococcus* (seen in 14%) and *Klebsiella* species like most other studies were the second most common. *Klebsiella* infections being more common among postnatal women as compared to antenatal women (7.3 vs. 4.9%) could reflect the presence of a hospital-acquired infection in postnatal women. The spectrum of uropathogens was largely similar in both antenatal and postnatal samples.

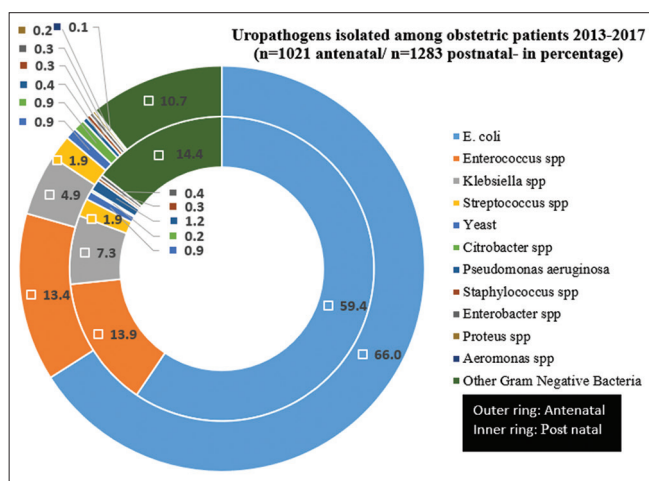
The increase of the prevalence of multidrug-resistant organisms is always a challenge and is also specific to each geographical region. It is the regional susceptibility data that guide the appropriate use of antibiotic treatment. Nitrofurantoin with its excellent sensitivity remained the best choice for asymptomatic or lower UTI. However, it is known that this drug is not useful when women with UTI

have systemic signs and symptoms. The sensitivity data suggest that nearly 30% of antenatal and 40% of postnatal *E. coli* isolates could be potential ESBL producers. This study showed 80–90% sensitivity with use of gentamicin for Gram-negative bacilli and could still be used as first-line management in acute pyelonephritis in pregnancy before cultures sensitivity reports are available. Good susceptibility of uropathogens to amoxicillin made it a convenient drug to use in UTI with Gram-positive enterococcal infection.

The strength of our study is that the large amount of data collated over 5 years. The limitations of our study are that it is a retrospective study from a large tertiary center where even though most of the women revisited the hospital with their complications, there may be considerable under reporting, and therefore, the prevalence of UTI may not be accurate. The data were collated from laboratory and hospital records of women having for antenatal and postnatal care.



**Figure 2:** Time period for the development of UTI in the (a) antenatal period and (b) postnatal period.



**Figure 3:** Uropathogens isolated in urine cultures among obstetric patients.

Antimicrobial stewardship is an important aspect of healthcare and a heightened awareness of susceptibility patterns of common uropathogens to commonly used antibiotic is paramount for rational drug use in pregnancy. This study has made us aware of the bacterial profile and its sensitivity to commonly used antibiotics in our setting.

## CONCLUSION

Thus, the importance of microbiological evidence prior to administration of antimicrobials is evidenced by 79% negative cultures in this 5-year cohort. About 9.5% culture

positivity among antenatal and 13.28% among postnatal patients may be expected with Asymptomatic bacterial carriage (ASB) 2.1% of the antenatal cases in this region and 40% of all significant culture growths. *Escherichia coli* accounted for 60-66% of significant bacteriuria followed by *Enterococcus* and *Klebsiella* species with 30-40% *E.coli* probable ESBL producers. Nitrofurantoin followed by amoxicillin-clavulanate were found to be the best oral antimicrobial options.

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## Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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