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Asymptomatic bacteriuria and drug sensitivity patterns during pregnancy in an Indian Teaching Hospital

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Abstracts
Background: *In pregnant women UTI is a major cause for complications during carrying period. It can be solved by proper antibiotic therapy, but without culture sensitivity reveals multi drug resistance strength in empirical therapy.*
Materials & Method: *Urine samples were collected from UTI pregnant women attending at Out Patients Department of Obstetrics and Gynaecology. Then samples were cultured and identified the organisms with respect to morphology and biochemical tests. Antibiotic sensitivity patterns were carried out with prescribed antibiotics disc in disc diffusion method.*
Result: *The maximum UTI found on the age group of 30-39 years. E.coli is the most organism followed by S.aureus in this study.*
Ceftriaxone and Cefixime was the most susceptible antibiotic for UTI in the pregnant women.
Conclusion: *Routine microscopic and culture should be carried out in pregnant UTI women and before empirical therapy culture sensitivity must be carried out to minimize the resistance organism.*
Keywords: *UTI, Resistant, Pregnant, antibiotics, E. coli.*

Introduction

Urinary tract infections (UTI) are common women and it is very common during pregnancy due to hormonal and anatomo-physiological changes that facilitate the growth and dissemination of bacteria in the maternal urinary tract[1]. From literatures, it is revealed that 5–10% of women suffer some kind of UTI during pregnancy[2]. The most common situation is Asymptomatic bacteriuria followed by acute cystitis and pyelonephritis[3]. If the proper treatment will not carried out then serious consequences for maternal and fetal health will be revealed[1]. Due to short urethra and its anatomical

proximity to the anal orifice, UTI are more prevalent in women[4,5]. The bacteria is the most causative organism for UTI which complicates pregnancy[6]. In the body Pregnancy causes numerous hormonal and mechanical changes. Ninety percentage of the pregnant females suffer urethral dialatation increasing the risk of urinary stasis and vesicouretral reflux, It start in the sixth week, with peak incidence during 22nd to 24th weeks[7]. The pregnancy are additional factors to facilitate bacterial growth during glycosuria and aminoaciduria[8]. Untreated leads to maternal and perinatal morbidity and mortality left pregnancy in UTI[9].The pregnancy is associated with low birth weight and premature delivery during untreated bacteriruia[10], as pregnant women's have UTI is the common health problem[11].

UTI is important for successful treatment and prevention of complications. However, the antibiotic-resistant urinary pathogens are increasing prevalence, an appropriate empirical agent is increasingly difficult. The clinical practice guidelines are reflected in 2010, which recommend using nitrofurantoin as a first-line agent in place of cotrimoxazole, owing to a rise in the occurrence of organisms resistant to the latter [12,13]. In the treatment of UTI is used resistance to other antimicrobials, also fluoroquinolones is increasing particularly, the prevalence of extended-spectrum-beta-lactamase (ESBL) is producing *Enterobacteriaceae* and multidrug-resistant (MDR) *Pseudomonas aeruginosa*[14-16]. The urinalysis results consider the choice of antimicrobial agents should be preferably, the pathogen identification is allow, The susceptibility of microorganisms indicates to specific groups of antimicrobials in addition to antimicrobial susceptibility testing[17]. However, the antimicrobial agent is correct choice to treat UTI during pregnancy is complex because it requires full safety to maternal and fetal, in addition to gradually of use, access, and cost of treatment[18]. In recent years the uro-pathogens has been reported globally by development resistance to effective antibiotics previously[19,20], and the place and time are vary susceptibility[21].The protection of fetus and resistance development of uropathogens are two major challenges while treating UTIs in pregnancy. While prescribing antibiotics, the physicians must consider possible side effects from drugs to protect maternal and fetal safety[22,23]. The antibiotic chosen should have efficacy and low resistance rates in a given population at the same time[24,25].

The normal vaginal, perineal, and fecal flora are cause of the UTI [26,27]. They include species of *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus faecalis*, *Proteus mirabilis*, *Klebsiella* species and *Streptococcus* species and others[28]. The UTI causing organisms have been reported to resistance antibiotics[27]. The broad spectrum antibiotics use frequently, these resistant bacteria is mainly due to widespread use of antibiotics in people and animal feeds[29,28]. These resistance properties are easily transferred among the bacteria of different genera through plasmids and other means[27]. Although they are still seen in community acquired UTI with an increasing presence of gram-positive cocci like *Staphylococci* and gram negative organisms like *Klebsiella* becoming more frequent and the resistance of antibiotics are mostly observed in hospital[30,31].

Without the use of a urine culture or susceptibility testing to guide therapy, current management of UTIs are usually empirical. However, the community acquired many infections, antimicrobial resistance between the pathogens that cause UTIs is increasing and is a major health problem in the treatment of UTI[32,33]. The antimicrobial resistance is growing worldwide, particularly *E.coli* is the dominant causative agent of UTI in pregnant women [34].

Materials & Methods

Different urine samples from pregnant women with or without having symptoms of UTI were collected during October 2014 to January 2016. The age of people included in the study ranged from 25-40 years. Verbal informed consent from

target population and approval from institutional research ethical committee were obtained before starting the experiment. Female patients aged between 25-40 years with uncomplicated UTI symptoms like frequency, urgency and dysuria were included in the study. Pregnant women on antibiotics within the last 2 weeks and those who could not give consent to participate in the study were excluded. Clean catch midstream urine samples were collected into a sterile screw capped universal container by standard method. The samples were labeled and 0.2 mg of boric acid was added to prevent the bacterial growth in urine samples. The samples were cultured on cysteine-lactose electrolyte deficient agar and blood agar using a sterile 4 mm platinum wired calibrated loop for the isolation of microorganisms. The plates were incubated for overnight at 37 °C and the samples were considered positive when an organism was cultured at a concentration of 104 CFU/mL which was estimated through multiplying the isolated colonies by 1 000. The isolates were identified up to the species level by standard biochemical tests[15]. Antibiotic sensitivity testing was performed by the modified disc diffusion method as per the recommendations [16]. Inoculums adjusted to 0.5 McFarland standard was swabbed on Mueller Hinton agar plates for antibiotic sensitivity assay. Eight groups of antimicrobials such as penicillins, cephalosporins, fluoroquinolones, aminoglycosides, macrolides, lincosamides, glycopeptides and sulfonamides were selected based on frequent prescription and used in this study. Among the group, the antibiotics tested were amoxicillin (10 µg), oxacillin (10 µg), cloxacillin (5 µg), cefotaxime (10 µg), ceftriaxone (30 µg), nalidixic acid (30 µg), ciprofloxacin (5 µg), norfloxacin (10 µg), amikacin (30 µg), gentamycin (10 µg), erythromycin (10 µg), clindamycin (2 µg), vancomycin (30 µg) and co-trimoxazole (30 µg). Statistical analysis was done using Chi-square test and student's t-test.

Results

A total number of 288 urine sample from pregnant women were screened for bacterial contamination. The pregnant women were age from 20 to more than 40 years old. Among the 288 samples 186 urie were infected (64.483%).It is revealed that in the age group 30-39 maximum contamination were found.(Tab-1).

Different bacteria were isolated from UTI samples *Escherichia coli*-113 (Fig 1), *Staphylococcus aureus*-94, *Pseudomonass* pp-76, Coagulase negative Staphylococci-69, *Candida barbicans*-37, *Klebsiellas* pp-13, *Proteus* spp-05, *Enterobacters* pp-04, *Streptococcus* spp-03.(Tab-2).

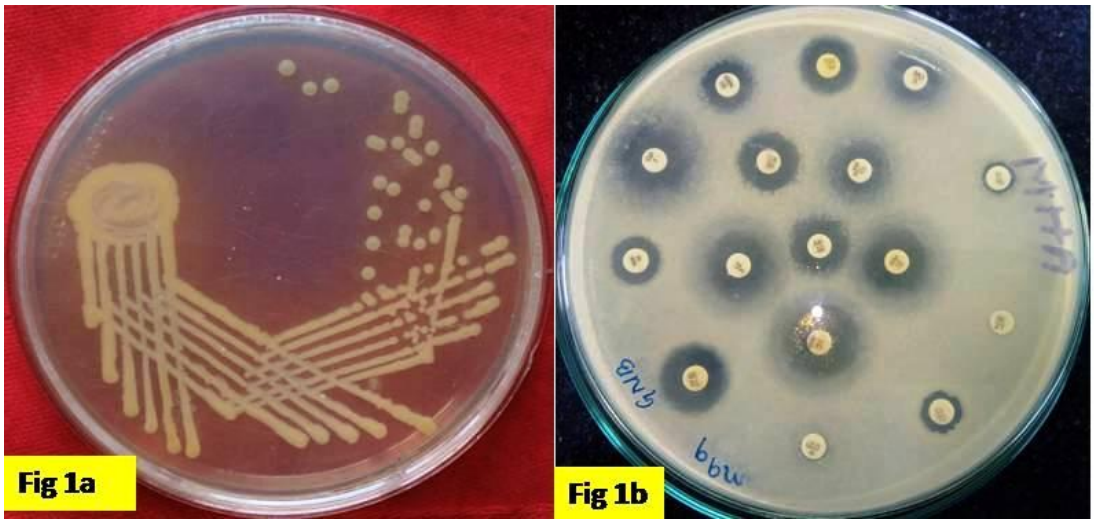

Fig 1a Pure culture of *E. Coli*, **1b.** Antibiotic sensitivity pattern of *E. coli*

All the isolated bacteria were tested for antibiotic sensitivity pattern with prescribed 51 antibiotics among them. It was revealed that NET was resistance to Escherichia coli-37.5%, Staphylococcus aureus-23%, Pseudomonass pp-50%, Coagulase negative Staphylococci-50%, Candida barbicans-20%, Klebsiellas pp-58.3%, Proteus spp-7.31%, Enterobacters pp-25% and Streptococcus spp-33.3% respectively .Tab-3(a),3(b) & 3(c).

Table 1 Distribution of microbial isolates in the urine of pregnant women with respect to age

Serial Number	Age range	Number examined	Number infected	Percent (%)
1.	<20	17	2	11.765
2.	20-29	116	72	62.069
3.	30-39	149	107	71.812
4.	>40	6	5	83.333
5.	total	288	186	64.583

Table 2 Number of organisms isolated from urine samples from pregnant women

Microbial isolates	Microbial isolates in frequency (n=414)	Percentage of Microbial isolated
Escherichia coli	113	27.29
Staphylococcus aureus	94	22.71
Pseudomonass pp	76	21.01
Coagulase negative Staphylococci	69	16.67
Candida barbicans	37	8.94
Klebsiellas pp	13	3.14
Proteus spp	5	1.21
Enterobacters pp	4	0.97
Streptococcus spp	3	0.72

In this study 51antibiotics were used for UTI in pregnant women. It is revealed that Ceftriaxone (CTR) and Cefixime (CFM) Antibiotics were most resistance 39.39%. However, the antibiotics CPZ, PAZ, FUR, CD, PB, CPT, ERY, AMX, TI, C, RIF, NAL, DOR and LNC were list resistance (Tab-4).

Table 3(a): Microorganism Resistance Percentage

Microrganisms	AMK	AMC	CEF	GEN	NOR	NIT	PIT	LNZ	AZT	OFL	CTR	CFM	CPM	LVF	VAN	TBR
Escherichia coli	37.5	12.5	62.5	12.5	16.5	24.5	0	12.5	50	12.5	15	19.5	12.5	0	12.5	13
Staphylococcus aureus	23	34	12	43.5	0	100	12	17	23	15	32	21	0	19	22	15
Pseudomonass pp	50	25	25	50	25	0	50	50	25	50	0	25	100	50	75	25
Coagulase negative Staphylococci	50	25	25	50	25	100	0	25	0	25	50	0	50	25	50	75
Candida barbicans	20	40	0	20	80	40	40	20	20	40	0	40	40.5	20	80	0
Klebsiellas pp	58.3	41.6	8.3	58.3	8.3	16.6	8.3	8.3	58.3	8.3	16.6	27.6	28	66.6	8.3	12.5
Proteus spp	7.31	31.7	19.5	4.87	78	12.1	24.3	0	0	58.5	19.5	29.2	4.8	4.8	0	4.8
Enterobacters pp	25	25	75	50	0	25	100	25	25	50	25	25	25	50	75	50
Streptococcus spp	33.3	23.3	33.3	0	33.3	26	33.3	0	23	33.3	62	42	0	46	12.6	13.5

Table-3(b): Microorganism Resistance Percentage

Microrganisms	NET	PEP	PEN	AMP	CAZ	IC	CFS	CAC	CPZ	LNC	PAZ	OXC	FUR	TGC	CD	TEC	CXM	CIS
Escherichia coli	12.5	0	12.5	0	12.5	50	25	12.5	12.5	75	0	37.5	0	75	37.5	0	37.5	12.5
Staphylococcus aureus	42	12	14	19	14	27	0	19	27	14	63	73	0	0	19	47	0	38
Pseudomonass pp	25	50	25	50	0	25	25	50	0	25	75	50	0	25	0	25	50	0
Coagulase negative Staphylococci	75	0	12.5	50	25	25	50	25	0	12.5	25	75	12.5	0	50	25	25	75
Candida barbicans	20	20	60	0	20	0	40	20	60	0	80	0	20	40	60	0	20	20
Klebsiellas pp	16.6	8.3	44	8.3	33.2	8.3	0	33.2	16.6	8.3	0	74.3	8.3	16.6	0	8.3	8.3	8.3
Proteus spp	4.8	21.9	0	4.8	17	0	9.75	14.6	9.75	28.8	9.6	2.43	0	19.2	43.2	4.8	4.87	4.87
Enterobacters pp	12.5	12.5	50	0	50	20	0	25	25	75	0	100	25	0	75	50	25	0
Streptococcus spp	33.3	0	33.3	66.6	33.3	0	11.1	33.3	0	19.6	43.3	23.3	11.1	13.3	0	33.3	66.6	66.6

Table-3(c): Microorganism Resistance Percentage

Microrganisms	IMP	CIP	PB	MRP	CPT	ERY	CFP	COT	CIT	COL	AMX	CN	TI	C	RIF	NAL	DOR
Escherichia coli	12.5	62.5	12	0	25	12.5	12.5	50	0	12.5	12.5	50	62.5	75	0	12.5	50
Staphylococcus aureus	14	19	0	17	13.5	29.6	43.5	100	0	48	23	13	16	0	19	34	0
Pseudomonass pp	0	50	0	25	0	50	0	12.5	25	25	75	0	12.5	0	12.5	0	12.5
Coagulase negative Staphylococci	12.5	0	25	50	50	0	12.5	100	12.5	50	50	12.5	12.5	0	50	0	50
Candida barbicans	60	20	0	40	20	20	60	80	0	20	0	40	0	40	0	60	20
Klebsiellas pp	49.8	66.6	8.3	8.3	0	16.6	24.9	8.3	8.3	0	8.3	0	33.2	0	49.8	8.3	0
Proteus spp	2.43	26.8	0	2.43	43.9	19.4	0	43.9	2.43	2.43	0	19.4	43.9	2.43	26.8	19.4	2.43
Enterobacters pp	50	12.5	12.5	0	75	50	50	25	0	12.5	25	25	12.5	0	12.5	50	50
Streptococcus spp	11.1	33.3	0	66.6	33.3	11.1	0	33.3	22.2	0	23.3	0	0	33.3	66.6	11.1	33.3

Table-4: Antibiotics Resistance And Percentage

SL.NO.	Antibiotics	Resistance	% Of Resistance	26	PAZ	0	0
1	AMK	19	14.28	27	OXC	5	0
2	AMC	20	15.03	28	FUR	0	3.75
3	CEF	17	12.78	29	TGC	1	0
4	GEN	11	8.27	30	CD	0	0.75
5	NOR	39	29.32	31	TEC	1	0
6	NIT	13	9.77	32	CXM	2	0.75
7	PIT	18	13.53	33	CIS	4	1.5
8	LNZ	1	0.75	34	IMP	1	3
9	AZT	11	8.27	35	CIP	28	0.75
10	OFL	30	22.55	6	PB	0	21.05
11	CTR	13	39.39	37	MRP	2	0
12	CFM	13	39.39	38	CPT	0	1.5
13	CPM	7	5.26	39	ERY	0	0
14	LVF	10	7.51	40	CFP	1	0
15	VAN	2	1.5	41	COT	25	0.75
16	TBR	1	0.75	42	CIT	3	18.79
17	NET	6	0.75	43	COL	2	2.25
18	PEP	18	4.51	44	AMX	0	1.5
19	PEN	9	13.53	45	CN	4	0
20	AMP	1	6.76	46	TI	0	3
21	CAZ	9	0.75	47	C	0	0
22	IC	1	6.76	48	RIF	0	0
23	CFS	7	0.75	49	NAL	0	0
24	CAC	9	5.26	50	DOR	0	0
25	CPZ	0	6.76	51	LNC	0	0

Discussion

Clinical diagnosis and empiric antibiotic therapy of UTI among pregnant women lead to massive antibiotic misuse, inadvertently rendering the first line of drugs ineffective. Diagnostic tests, easy to carry out and evaluate also by inexperienced staff, are therefore necessary. In this study, we investigated a total of 2 562 patients for bacteriuria. Of these 1 621 were urine samples from pregnant women in IMS and SUM Hospital, Bhubaneswar with and without UTI symptoms, in order to verify the prevalence of cystitis and ABU. Because physiological changes during pregnancy might cause symptoms similar to cystitis, a low frequency of bacteriologically confirmed UTI among patients with symptoms was anticipated. Although the prevalence of UTI among pregnant women in our study is close to those reported regionally[17,18], it is particularly alarming that our observations show that as many as 96% of patients are routinely treated with antibiotic therapy that they do not require. The positive correlation between antibiotic misuse and development of drug resistance[35] may in part explain the high antibiotic resistance seen in developing countries as we and others have demonstrated[36,37]. To improve the diagnosis, we evaluated nitrite and leukocyte esterase tests and a simplified culture method, dipslide. In line with previous reports, nitrite and leukocyte esterase tests alone demonstrated insufficient diagnostic value in this study. The combined results of these 2 tests demonstrated acceptable specificity and low sensitivity but were still of limited value. Although the nitrite test had high specificity, the sensitivity was low, especially among pregnant

women, which is line with other studies[38] and may relate to frequent urination leading to reduced bacterial concentration. Further, presence of vitamin C in urine is another confounding factor[39], which cannot be ruled out among our patients. During pregnancy, the specificity of urinary leukocytes as an indicator for bacteriuria per se might be questionable because of elevated urine specific gravity that may give false negative results[39]. Similarly, low sensitivity was obtained in urine samples collected from non -pregnant women. Moreover, false negative results have been reported with common antibiotics like cephalosporins[40]. Also, the poor correlation between enzymatic activity and microscopic detection of leukocytes in urine is a major concern. Even though microscopy is regarded as the golden standard for this analysis, high variability between replicate leukocyte counts suggest that the analysis suffers substantial draw backs, when performed in the clinical setting. Moreover, false negative results might be due to cell lyses if analysis is delayed. In addition, microscopic analyses of leukocyturia are time consuming if carried out with care. Taken together, detection of leukocytes especially using microscopy but also leukocyte esterase test are poor markers for the detection of UTI particularly among pregnant women and is in line with previous studied[41,42]. The use of dip slide culture was, on the other hand, particularly rewarding in urine samples with no bacterial growth. These samples constitute the majority and were correctly diagnosed. Therefore, even in the hands of inexperienced healthcare providers this would substantially decrease the antibiotic use. The identification of *E. coli* and other Enterobacter-iaceae was also satisfactorily evaluated with the dipslide test even with inexperienced medical doctors and nurses. This can in part be attributed to the *E. coli*–specific agar containing β glucuronidase, resulting in a color change. However, false negative results can occur in rare cases if the strain lacks the enzyme [13]. Also, false positive results may occur among *Citrobacter* spp.[43]. Interestingly, we demonstrated that nurses with very limited training, and with no access to a professional microbiological laboratory or expert personnel, correctly diagnosed *E. coli* UTI in almost 80% of cases. To accurately define mixed fecal flora using dip slide[44] was problematic, and the nurses prescribed antibiotics in 91% of such cases. In the current study, contamination was observed in 5%, whereas others have demonstrated up to 10%[45], which would implicate risk of over interpretation. Another drawback for dipslide culture especially among pregnant women is the failure to detect GBS, which is in line with observations made employing 2-medium dip slides[46]. Treatment recommendations differ between countries. In IMS and SUM Hospital, Bhubaneswar, pregnant women with UTI receive amoxicillin, amoxicillin/clavulanic acid, or cephalexin without laboratory verification and susceptibility testing, whereas nitrofurantoin or amoxicillin are recommended in Kenya, Tanzania, and Rwanda [47–49]. The use of nitrofurantoin and pivmecillinam are also recommended by international guidelines[50]. In our study, *E. coli* was highly resistant to many of the drugs used for treatment of pregnant women like 66% resistant to ampicillin (amoxacillin), 38% to amoxicillin/ clavulanic acid, and 18% to cephalexin, which decreases the treatment options. In addition, we report a high ESBL prevalence (18%), even higher than the general ESBL prevalence in Africa[51]. As a consequence, almost all pregnant women presenting with UTI symptoms will receive antibiotics either not indicated at all or with high risk of being ineffective. International and East African regional guidelines recommend nitrofurantoin and during the last 2 trimesters also pivmecillinam. An appropriate alternative would therefore be nitrofurantoin or pivmecillinam, where low resistance is observed[47-50].

The high antibiotic consumption proves the importance of continuously reviewing the susceptibility pattern of uropathogens. It also calls for diagnostic methods possible to use in clinics

with no access to laboratory service. To the best of our knowledge, this is the first study investigating the practicability of the dip slide culture test under clinically relevant conditions in a low-resource country. To introduce dip slide in clinical routine, possibly supported with nitrite and leukocyte esterase tests would substantially reduce the misuse of antibiotics. Healthcare professionals can learn to correctly evaluate samples with no bacterial growth. Compared to clinical diagnosis alone, the use of dip slide would imply substantially decreased antibiotic consumption and as a consequence decreased risk for development of resistance among bacterial pathogens. The massive amount of saved antibiotics might furthermore outweigh, at least in part, the costs associated with the increased diagnostic efforts.

Conclusions

In many clinicians choose for the strip urinalysis method for assessing urine in pregnant women and in many hospitals in developing countries, routine urine culture test is not carried out for antenatal patients. Which is usually seen in the case of culture test the true picture of such urine specimen cannot be fully assessed as the strip cannot quantify the extent of infection in such a patient as well as provide antimicrobial therapy. Usually antibiotics are given empirically before the laboratory the urine culture results are available. Their antibiotic susceptibility pattern is mandatory to ensure appropriate therapy, current knowledge of the organism that causes UTIs and. Therefore, The antibacterial activity is needed to periodic evaluation and update information. Therefore, including their antibiotic susceptibility pattern isolated from pregnant women with urinary tract infection to readdress this situation.

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