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EVALUATION OF ANTIMICROBIAL TREATMENT PRACTICES FOR URINARY TRACT INFECTIONS IN PREGNANT WOMEN IN TERTIARY CARE CLINICAL SETTINGS OF PAKISTAN

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ABSTRACT: Urinary tract infections (UTIs) are the most common infections of pregnancy and pose great therapeutic challenges. The objective of the present study was to evaluate and compare the antimicrobial treatment practices for UTIs during pregnancy in comparison with the standard treatment guidelines. A prospective cross sectional study was conducted on 782 pregnant female patients suffering from UTIs in hospitals of Wah Cantt, District Rawalpindi, Pakistan. Prescriptions and available laboratory test reports including complete blood count (CBC) from each patient was taken. Statistical tests One Way ANOVA and chi-square tests ($P \leq 0.05$) were performed to obtain the desired outcomes. It was evaluated that none of the clinical setting have developed its own antibiogram or local antibiotic use guidelines. Standard management guidelines for antimicrobial therapy for UTI in pregnancy were followed in only 16.7% patients. Moreover only two drugs from the standard management guidelines were prescribed to the patients. It was determined that statistically significant population ($p < 0.05$) were being prescribed with the drugs not recommended by any guidelines. 26.9% patients were being prescribed category “C” drug. One of reasons for not prescribing the 1st line drug is its shortage in Pakistan regardless of being part of essential drug list of Pakistan. Appropriateness of antibiotic prescribing is also affected by using pregnancy category “C” drugs ($p < 0.05$). It is recommended that safe prescribing practices should be adopted and patients should be monitored closely for desired clinical outcomes. The Drug Regulatory Authority of Pakistan (DRAP) should ensure the availability of essential medicines in country.

INTRODUCTION: Urinary tract infections (UTIs) are the second most common disorder which arises during the duration of being pregnant ¹. Females are at greater risk for development of UTIs due to shorter length of urethra.

The probability of UTIs are augmented multiple folds during pregnancy due to anatomical and physiological changes in the uterus, weight of the fetus on the bladder, increased bladder volume and muscles tone.

Unhygienic practices and urinary secretions may further pose a threat towards progression of infection ². The incidence of UTI during pregnancy is 5 - 10% ³, and a review reported approximately 5% of hospital admission of such cases ¹. In developing countries like Pakistan where a large

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number of populations is earning below the per capita income as defined by World Bank and living below the poverty line without any facility for health insurance, factors including poor diet intake, difficult access to tertiary health facilities and physicians may come into play leading to occurrence of several complications during pregnancy. UTIs during pregnancy can lead to serious complications like pyelonephritis or acute renal failure in the presence of these factors if not managed properly⁴.

The *Escherichia coli* a common pathogen, reported with incidence up to 95% for pyelonephritis^{5, 6, 7}. The both strains of microorganisms of Gram-negative and gram-positive are occasionally found for example *Proteus mirabilis*, *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Citrobacter*, *B. streptococcus* (GBS) and *Staphylococcus saprophyticus*⁵. 10-15% of pregnant women are found with *Gardnerella vaginalis* and *Ureaplasma ureolyticum* in the bladder urine; however, their clinical consequence is unclear⁸.

The UTIs are one of the major causes of fetal and maternal complications during gestation period. It is observed that in the presence of pyelonephritis, the risk for pre-mature delivery is increased. Infants with low birth weight, and fetal mortality rate are also elevated^{9, 10, 11}. Pyelonephritis is associated with Preeclampsia, gestational hypertension, anemia, thrombocytopenia, transient renal insufficiency, and postpartum endometritis in pregnant women^{9, 11, 12, 13}.

In usual prescribing practices, antibiotics are prescribed empirically without considering urine culture results. During pregnancy, the antimicrobial chosen should have a good maternal and fetal safety profile, excellent efficacy and low resistance rates. It is important to screen, raise suspicion and know how to recognize this condition, intending to promptly initiate appropriate treatment in order to minimize complications associated with UTI.

To establish the rational drug use, rational prescribing is an essential tool. According to WHO, about half of all medicines are prescribed, dispensed or sold inappropriately and also taken incorrectly. Irrational drug prescribing usually leads to increased chances of treatment failure,

antimicrobial resistance in case of antibiotics and social and economic burden on patient as well as on community as a whole. WHO and other standard guidelines always emphasize on the use of essential drugs with their generic names for the disease treatment^{14, 15}.

The present study was conducted to determine the antibiotics use pattern and its appropriateness in urinary tract infections in tertiary care hospitals and to compare with the standard treatment guidelines along with different factors influencing the overall clinical outcomes. This type of study will help the policy makers and clinicians to develop SOPs and guidelines for improving rational prescribing.

MATERIALS and METHODS:

Study Design: This was an observational prospective cross sectional study focused on pregnant females with UTI.

Study Populations: The study population included pregnant women attending Ante Natal clinic at different hospitals of Wah Cantt. District Rawalpindi, Pakistan.

Sample Size and Sampling Techniques: Sample size was calculated by WHO approved software EPI info 7.1.5 which was 782 patients according to birth rate and population of the area. Wah Cantonment is a military city which is located in Punjab province, with a highest literacy rate (98%), 30 km to the north west of Rawalpindi/Islamabad. Total population of Wah Cantt is 198,891 (1998), so random sampling was done¹⁶. Convenience sampling technique was applied to select the desired sample.

Inclusion Criteria:

- Pregnant females,
- Having any trimester,
- Having symptoms of UTI.

Exclusion Criteria:

- Pregnant female with lower abdominal pain by any specific reason other than UTI.
- Pregnant ladies in labour.
- Non pregnant women with symptoms of UTI.

Study Area: This study was conducted in the tertiary clinical settings of 16 different hospitals of Wah Cantt District Rawalpindi.

Study Period: The study was conducted from December 2014 to May 2015.

Study Tool: A clinical checklist was developed after a thorough literature review and extensive review of various clinical guidelines for management of UTI in pregnant females. A raw checklist was developed initially which was subjected to face and content validation through focus group discussion with research colleagues and supervisors specializing in clinical data analysis. The parameters finally selected to be recorded in checklist included weight, age, systolic and diastolic blood pressure, number of trimester, hemoglobin level, record of prescribed medication including dose, duration, frequency and use of supplement for management of UTI.

Following guidelines were studied to identify the standard treatment protocols and to develop the clinical checklist:

1. Health Protection Agency (HPA),
2. British society for Antimicrobial Chemo Therapy (BSAC),
3. Scottish Intercollegiate Guidelines Network (SIGN) 2012,
4. The UK Teratology Information Service.2008 (UKTIS),
5. National Institute for Health and Care Excellence (NICE),
6. American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin no.91,
7. Chronic kidney disease. NICE clinical guideline 73 (2008),
8. National Collaborating Centre for Women's and Children's Health, National institute for health and clinical excellence (NHS),
9. Infectious Diseases Society of America (IDSA),
10. European Society for Microbiology and Infectious Diseases (ESCMID),
11. The Infectious Disease Society of Pakistan (IDSP),
12. South Australian Perinatal Practice Guidelines,
13. King Edward Memorial Hospital Guidelines (KEMH) Australia,

14. The Geneva Foundation for Medical Education and Research and World Health Organization (WHO) guidelines.

Research Approval and Consent: Research approval was granted from management of each hospital and informed consent was signed from each patient as well.

Data Collection: Data was collected directly from the prescriptions and available medical records from each hospital.

Data Entry: Data was recorded in Statistical Package for Social Sciences (SPSS) version 16.0 by defining each variable as nominal, ordinal or scalar based upon its type.

Data Analysis: SPSS 16.0 is used for data analysis and following tests were applied. The variables recorded in SPSS included the following as listed in **Table 1**.

TABLE 1: VARIABLES CHECKED

S. no.	Variables
1	Age of the patient
2	Weight of the patient
3	Trimester of patient
4	Blood Pressure of patient
5	Hemoglobin of patient
6	Name of Antibiotic prescribed
7	Dose of antibiotic prescribed
8	Frequency of Antibiotic prescribed
9	Duration of Antibiotic prescribed
10	Appropriateness of prescribed Antibiotic
11	Pregnancy category of prescribed antibiotic
12	Cost of antibiotic therapy

The treatment choices of all these standard guidelines for UTI in pregnancy are summarized in **Table 2**.

TABLE 2: SUMMARY OF TREATMENT FOR UTIs

Antibiotics	Duration of therapy	Comments
Nitrofurantoin 100 mg	Q 12 h for 3-5 days	Avoid in G6PD deficiency
Amoxicillin 500 mg	Q 8 h for 5-7 days	Causes resistance
Co-amoxicillin/ clavulanate	500 mg Q 12 h 5-7 days	
Cephalexin 500 mg	Q 8 h 3-5 days	Causes resistance
Fosfomycin 2000 mg	Only single dose	
Trimethoprim	Q 12 h for 5-7 days	Do not use in 1 st trimester

The data recorded was subjected to analysis using descriptive statistics using frequency, measure of central tendency and cross tabulation to describe the data and trend among the associated variables. Inferential statistical tests including one way analysis of variance (ANOVA) and chi-square test was applied to determine statistical significance

among numerical and non-numerical variables respectively.

RESULTS: The antibiotics prescribed in the prescriptions along with its FDA pregnancy category collected from hospitals are listed in **Table 3**.

TABLE 3: LIST OF ANTIBIOTICS ACCORDING TO PRESCRIPTIONS

S. no.	Name of the antibiotic	Dose	Class of antibiotic	FDA category
1	Amoxicillin	500 mg	Cell wall synthesis inhibitor	B
2	Pipemidic acid	400 mg	DNA gyrase inhibitor	B
3	Enoxacinsesquinate	400 mg	Fluoroquinolone	C
4	Erythromycin	250 mg	Protein synthesis inhibitor	B
5	Co-Amoxiclav	625 mg	Cell wall synthesis inhibitor	B
6	Cefixime	400 mg	Cell wall synthesis inhibitor	B

Evaluation of Patients Regarding Appropriateness of Antibiotics: The appropriateness of antibiotics was checked according to standard treatment guidelines. The results of appropriateness of antibiotic prescribing as per the guidelines are listed in **Table 4**. The results calculated were also represented in **Fig. 1**.

(16.6%) were prescribed antibiotics which were appropriate according to standard criteria while 652 patients (83.4%) were given antibiotics other than standard treatment guidelines.

TABLE 4: APPROPRIATENESS OF THE ANTIBIOTICS

Result	Frequency	Percent
According to standard guidelines	130	16.6%
Not according to standard guidelines	652	83.4%

Frequency / Type of Antibiotic Prescribed to patients: In order to check patients receiving which antibiotics, comparison was made between antibiotics prescribed and percentage of patients which is shown in **Table 5** as well as in **Fig. 2** in graphical form. None of the patient was prescribed with the antibiotics as mentioned in the standard guidelines such as nitrofurantoin, cephalixin and fosfomycin.

The results showed in **Table 4** indicate that out of total 782 patients studied; only 130 patients

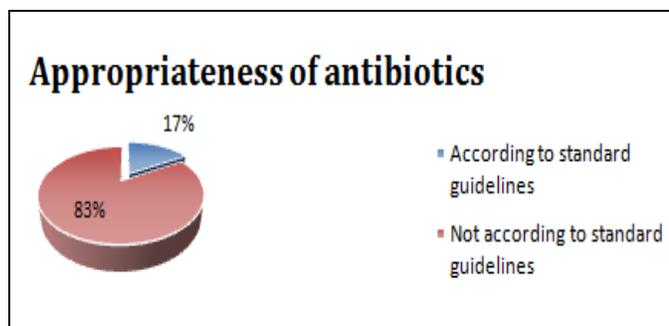


FIG. 1: ANTIBIOTICS APPROPRIATENESS

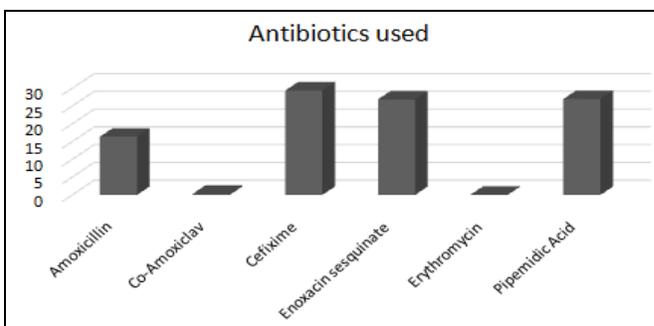


FIG. 2: ANTIBIOTIC USE AMONG PATIENTS

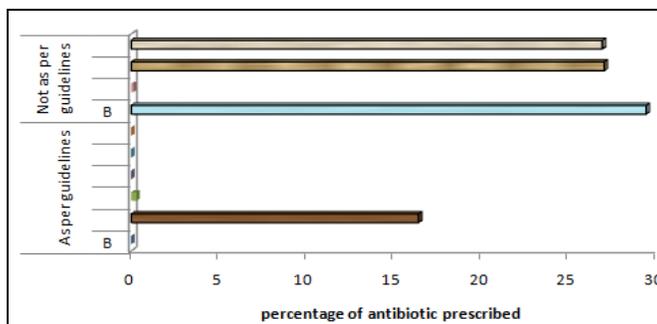


FIG. 3: GRAPH SHOWING PERCENTAGE OF EACH ANTIBIOTIC PRESCRIBED ALONG WITH ITS RATIONALITY OF USE AND FDA PREGNANCY CATEGORY

TABLE 5: NAME OF ANTIBIOTIC / PERCENTAGE OF PATIENTS

Therapeutic choice	Pregnancy category	Name of antibiotic	n (%)
As per guidelines	B	Nitrofurantoin	0 (0%)
		Amoxicillin	128 (16.4%)
		Co-amoxicillin/ clavulanate	2 (0.3%)
		Cephalexin	0 (0%)
		Fosfomycin	0 (0%)
Not as per guidelines	C	Trimethoprim	0 (0%)
	B	Cefixime	230 (29.4%)
		Erythromycin	1 (0.1%)
	C	Pipemidic acid	211 (27%)
		Enoxacinsesquinat	210 (26.9%)

Use of Antibiotics Related to FDA Category:

FDA has classified the antibiotics used during pregnancy which is based upon the adverse effects of these antibiotics on the pregnant women. The choice of the antibiotics should be according to this classification. Chi-square test concluded that appropriateness of antibiotic prescribing is affected by using pregnancy category "C" drugs ($p < 0.05$) and that the overall clinical outcomes cannot be achieved if pregnancy category "C" drugs are used. These results are shown in graphical form in **Fig. 3**.

DISCUSSION: It was observed that none of the hospital / clinic has developed its antibiogram or guidelines for use of antibiotics against the WHO recommendation. The usual trend of antibiotic prescription was based on individual physician choice without considering the level of antibiotic resistance or susceptibility.

It was also observed that no patient was prescribed 1st line antibiotic (*i.e.* nitrofurantoin, fosfomycin and cephalexin) choice in the treatment of UTI during pregnancy. It was further noticed that antibiotics were being prescribed to patients with symptoms of UTI without any prior screening tests. The cost of screening tests for UTI is to be borne by the patients themselves therefore they are reluctant to get these tests done on the advice of physicians. This reason compels the physicians to prescribe empirical therapy based on their past experiences.

Furthermore, most of the patients were being treated with 2nd or 3rd line antibiotics. One reason for not prescribing the 1st line drugs included shortage of nitrofurantoin and fosfomycin in the local market regardless of the presence of this drug in the essential drug list of Pakistan¹⁷.

Nitrofurantoin is also present in the essential list of medicines by WHO¹⁸ and also mentioned on the Pakistan Pharmacy Council website in the list of medicines that should be available in Pakistan². One reason for shortage of this drug in Pakistan is lack of profit margin in this drug due to its low price¹⁹. The results showed in **Table 5** indicate that out of total 782 patients studied; only 130 patients (16.6%) were prescribed antibiotics which were appropriate according to standard criteria while 652 patients (83.4%) were given antibiotics other than standard treatment guidelines.

It can be observed that only two drugs from the standard guidelines were prescribed to 16.7% patients only, while the rest of 83.3% patients were prescribed drugs which were not recommended by any clinical guidelines as first line therapy. It was determined that statistically significant population ($p < 0.05$) were being prescribed with the drugs not recommended by any guidelines. 26.9% patients were being prescribed with pregnancy category "C" drug *i.e.* enoxacinsesquinat which is not recommended drug according to the guidelines. The pregnancy category "C" drugs may show adverse effects to the fetus as proved from the animal studies²⁰.

CONCLUSION: It was evident from this study that there is a vast difference between the antibiotic prescribing pattern and clinical guidelines. None of the patient under study was prescribed 1st line drug mainly due to its shortage in local market regardless of being part of essential medicine list. The drug regulatory authority of Pakistan (DRAP) should ensure the availability of this and all other important drugs. Pregnancy category C and D drugs should be avoided in all patients until the risk to benefit ratio is determined because their use cannot only affect the desired clinical outcomes but can pose threat to the fetus as well.

The prescribing in 1st trimester should be most critically monitored since this phase can lead to irreversible damage to the fetus. As pregnancy is a critical condition; both the mother and fetus are at higher risk during this phase. Negligence and careless prescribing trends cannot only result in therapeutic failure but can result in permanent abnormality, premature delivery and abnormal growth of the fetus.

Recommendations: It is recommended that each hospital should follow the international guidelines to prescribe the medications. There should be proper screening tests before starting therapy. Empiric therapy should start only in such cases where it seems very necessary to give the antibiotics. The DRAP should make sure that all the medication which are enlisted in WHO essential list of medicines should be made available in Pakistan.

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CONFLICT OF INTEREST: Nil

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