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Research Article

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The Use of Fosfomycin is Suitable for Treatment of Urinary Tract Infection in Women during Second Trimester

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ABSTRACT

Background: Urinary tract infection in the form of asymptomatic or symptomatic disease is common during pregnancy and may cause obstetric complication that can be avoided by antibiotic treatment. Significant controversy is present in the published literature about the proper antibiotic and the sufficient duration to treat urinary tract infection during pregnancy.
Objective of the study: To investigate the efficacy of fosfomicin in treating urinary tract infection in a sample of pregnant women in their second trimester.
Patients and methods: Seventy pregnant women with urinary tract infection were enrolled in the current cross sectional study. They were classified into two groups; one given single dose fosfomicin and the other given cefuroxime.
Results: The cure rate using fosfomicn was comparable to the cure rate of cefuroxime, 85.7% versus 91.4%, with no statistical difference. No intolerable adverse effects were reported after using fosfomicin.
Conclusion: Single dose fosfomicin is efficient, safe, well tolerated antibiotic treatment for UTI in pregnant women during second trimester.

Keywords: UTI; Fosfomycin; Second trimester

INTRODUCTION

The clinical presentation of urinary tract infection during pregnancy may present as asymptomatic bacteriuria in which the diagnosis is made by urine culture in the absence of sound clinical features suggesting infection, acute symptomatic cystitis when infection is clinically obvious and usually limited to the urinary bladder or even as acute pyelonephritis when the kidney and renal pelvis is involved with obvious systemic signs of inflammation [1,2].

The incidence of asymptomatic bacteriuria, during pregnancy, in published literatures is variable but generally speaking it ranges from 2 to 10% and if left without treatment may it cause clinically overt cystitis or the more serious complication of acute pyelonephritis in a significant number of pregnant ladies [3-5].

The approved definition for the syndrome of women uncomplicated urinary tractinfection (UTI), by Food and Drug Administration in theUnited States, includes frequency, dysuria and / or urgency together with bacteruria and pyuria without underlying renal dysfunction or obstruction [6]. It has been shown, by the Royal College of Obstetricians and Gynecologists, In the United Kingdom, that nearly 50% of women have the experience of UTI for once at least during their lifetime. Inadequate treatment of UTI will eventually lead to pyelonephritis, and rarely may be complicated by septicemia, and periurethral abscess [7].

It has been reported that urinary tract infection during pregnancy is significantly associated with bad obstetric outcome like low birth weight and even preterm labor [1]. On the other hand urinary stasis during pregnancy may precipitate ascending of infection into renal pelvis and subsequently increasing the incidence of pyelonephritis making the treatment of symptomatic urinary tract infection and asymptomatic bacteriuria of prime importance to prevent such horrible complication [8].

After reviewing published database, thoroughly, we failed to find a clear consensus on the definite antibiotic choice and its proper duration [8,9]. Significant limitations on the choice of antimicrobial agents are caused by antibiotic-resistant *E. coli*, in particular when used in outpatients. Some authors declared that antibiotic resistant

E. coli strains was observed in 61% for ampicillin, 41% for co-trimoxazole, 30% for sultamicillin and 30% for co-amoxiclav [6]. One population survey, in Netherlands, showed that the isolation rate of urinary ESBL (extended spectrum betalactamase) *E. coli* strains had jumped from 0.1% to 1%($p<0.001$) in 5 years [10].

One of the serious problems during the last decade is the development, by several species of bacteria including those which are responsible for urinary tract infection (UTI), to obvious resistance to the previously well known efficient antimicrobial agents [1,11]. Another well recognized problem is that the rate of invention of new anti microbial agents is extremely low; however the use of old generation antibiotic may provide good choice for treating emergent resistant microbial agents; one such choice is fosfomycin [8]. The usual duration of traditional antibiotic therapy for the treatment of UTI is 7 to 10 days. A local study in2005 demonstrated a compliance rate of 82% only for short 3-day antibiotic treatment courses8. It was therefore hypothesized that single-dose treatment might inevitably improve patient compliance for UTI treatment and reduce the emergence of antibiotic resistance [6].

Fosfomycin is regarded as an old drug and was first discovered in Spain in 1969. Fosfomycin tromethamine is a highly water soluble salt, which has reliably good bioavailability following oral administration. It acts through inhibition of pyruvyl transferase, a cytoplasmic enzyme which catalyses the first step in the biosynthesis of peptidoglycans; it has abroad spectrum antimicrobial activity against the most frequent Gram-positive and Gram-negative bacteria encountered in UTIs. Additionally, distribution into tissues is good, achieving clinically acceptable concentrations in body fluids, kidneys and the bladder wall, and other organs. Compliance is not a problem with fosfomycin as it can be given as a single dose [12,13].

Several Studies in the United States and Europe pointed out that the cure rate for single fosfomcin is better than co-amoxiclav, norfloxacin and nitrofurantoin. In addition, fosfomycin was highly accepted by patients with little side-effects. It is prescribed as first choice antibiotic for acute uncomplicated cystitis, in German guidelines [14]. *E. coli* Antimicrobial susceptibility patterns should be considered in empiric antibiotic choice for the treatment uncomplicated UTIs [15]. There are substantial geographic differences among *E. coli* for in vitro susceptibility. In four large studies, rates of resistance were higher in US health centers than in Canadian health centers and greater in Spain and Portugal than other European countries [16-18]. Generally speaking, rates of resistance greater than 20 percent were registered in all regions for ampicillin, and in a lot of regions for trimethoprim. Fluoroquinolone resistance rates had been shown to be less than 10 percent in majority of North America and Europe regions,; however there was an obvious trend for raised resistance over time [19,20] Actually, in a study of *E. coli* outpatients urinary isolates in the United States, ciprofloxacin resistance rates were proved to rise from 3 to 17 % between 2000 and 2010 [19]. In a population-based study, carried out in Minnesota, of more than 5000 *E. coli* urinary isolates between 2005 and 2009, the incidence of bacteriuria with isolates resistant to fluoroquinolones and/or trimethoprim-sulfamethoxazole increased significantly [20].

So the aim of the current study was to investigate the efficacy of fosfomycin in treating urinary tract infection in a sample of pregnant women in their second trimester.

PATIENTS, MATERIALS AND METHODS

The current cross sectional study included 70 pregnant women with documented urinary tract infection via urinary culture. Those women were attending the obstetric outpatient clinic in Al-Diwaniyah maternity teaching hospital in Al-Diwaniyah province. The study extended from July 2015 through January 2016. The age range of those women was from 18 to 30 years. All the pregnant women were in their second trimester with a gestational age range of 13 to 19 weeks. They were classified into two age matched groups each of which consisted of 35 women. Women in the first group received single dose fosfomycin whereas the second group received the routinely used 5 days dose of cefuroxime. Cure was tested by repeating urinary culture following proper period of time. Statistical analysis was performed using statistical package for social sciences (SPSS) version 20 and Microsoft Office Excel 2010. Student t-test was used to investigate mean age and gestational age differences between the two groups while association between any two categorical variables was tested using Chi square and Fischer exact test after fulfilling proper statistical assumptions. The level of significance was chosen a $P\leq 0.05$.

RESULTS

The present study involved 70 pregnant ladies in their second trimester with urinary tract infection. They were classified into two groups; 35 women were treated with single dose fosfomicyn whereas the second group, 35 women, received standard 5 days course of ceferuxim.

The two groups were matched regarding mean age, 22.49 ±3.81 years versus 20.97 ±3.91 years (P=0.105) and mean gestational age, 15.57 ±1.38weeks versus 15.74 ±1.29 weeks (P=0.593), (Table 1).

Types of isolated microorganisms in both groups were shown in table 2; the most frequent microorganism was *E. coli* and there were no significant differences in the rates of *E. coli, Staph aureus, Enterobacter fecalis and Monilia*in in both groups (P>0.05).

The rate of cure in group 1 (on fosfomycin) was 85.7% whereas the cure rate in the second group (on ceferuxim) was (91.4%), nevertheless, no statistical significance was reported (P=0.707), Figure 1.
Follow up of the patients treated with fosfomycin revealed no remarkable side effects or complications.

Table 1: Mean age and gestational age of patients with UTI. Group 1: On single dose fosfomycin; Group 2: on cefuroxim; * Student t-test

Characteristic	Group 1 (n = 35)		Group 2 (n = 35)		P
	Mean ±SD	Range	Mean ±SD	Range	
Mother Age (years)	22.49 ±3.81	18 - 30	20.97 ±3.91	16 - 30	0.105*
Gestational age (weeks)	15.57 ±1.38	14 - 19	15.74 ±1.29	13 - 18	0.593*

Table 2: Isolated microorganism in both groups; Group 1: On single dose fosfomycin; Group 2: on cefuroxim; * Chi-square test "corrected"; †: Fischer exact test

Micro-organism	Group 1 (n = 35)		Group 2 (n = 35)		P
	N	%	N	%	
E. coli	30	85.7	30	85.7	1.000*
Staph aureus	1	2.9	4	11.4	0.353*
Enterobacter fecalis	1	2.9	1	2.9	1.000*
Monilia	0	0	3	8.6	0.239†

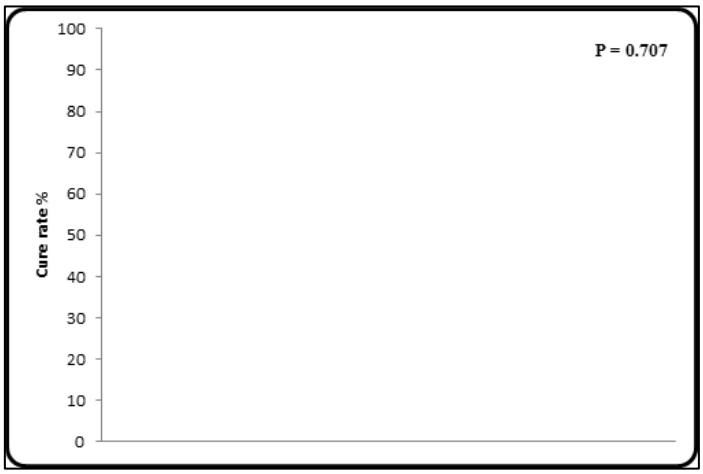

Figure 1: Comparison of cure rate in both groups

DISCUSSION

The current study showed that the most prevalent infectious microorganism in pregnancy related UTI was *E. coli* in agreement with [8,21,22] and followed by *S. aureus* in agreement with (Souzaa*et al*.,).
Greater than 95% of urinary tract infections are the result of a single bacterial species; *E. coli* is the most commonly seen infecting organism in acute UTI [23]. Staphylococci, Klebsiella, Proteus, Enterobacter, Pseudomonas, and Enterococci species are more frequently isolated from inpatients, while there is a greater occurrence of *E. coli* in outpatients. *Corynebacterium urealyticum* has been identified as an important nosocomial agent. Anaerobic micro-organisms are rarely encountered in the urinary tract. Coagulase Negative Staphylococci are a frequent cause of UTI according to some authors. *Staphylococci saprophyticus* may cause infection in young females of a sexually active age [24].
The present study came up with a cure rate for fosfomycin of 85.7% which is nearly similar to that reported by Souzaa*et al*. who reported a rate of 89% and also similar to Neuner *et al*. [25] who describe a rate of cure of 86%. Single dose fosfomycin was proved to be as efficient as cefruxime in treating UTI in pregnant women. High efficacy of fosfomycin during pregnancy was reported by several other authors [26-29].
It has previously been registered that fosfomycin has great *in vitro* activity against extended-spectrum beta-lactamase ESBL-producing *E. coli* [30]. Clinical researches have demonstrated fosfomycin to be active for the treatment of lower UTIs due to ESBL-producing *Enterobacteriaceae* [31]. Fosfomycin may be a promising antibiotic choice; however, high usage has been observed to correlate with raised resistance among ESBL-producing *E. coli* isolates [32].

On the other hand, the present study showed neither significant side effect nor obstetric complication by all women participating in study.

Adding the high efficacy of the drug in eradication of microorganisms involved in UTI, the lack of intolerable and or complications to the simple single dose of fosfamycin we can confidently recommend the use of this drug as the first choice for treating UTI in pregnant ladies during second trimester.

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