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ORIGINAL ARTICLE

A Comparative Study Between Cephalexin and Fosfomycin in the Treatment of Urinary Tract Infection During Pregnancy

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Abstract

Aim: **To compare between cephalexin and fosfomycin in the treatment of UTIs during pregnancy.**

Background: **Urinary tract infection (UTI) is one of the most common bacterial infections during pregnancy, which can have serious complications for the mother and the fetus. Therefore, effective management of the infection using serial antibiotics is important.**

Patients and methods: **This randomized controlled study was conducted on 200 women attended at the Obstetrics and Gynecology Department in Shebin El-Kom Teaching Hospital from October 2021 through April 2022. Patients were randomized into two groups: the (F) group: 100 cases treated with fosfomycin and (C) group: 100 cases treated with cephalexin.**

Results: **We revealed that pus cells in urine analysis before and after treatment did not show any significant difference between the two groups ($P > 0.05$). While pus cells in the urine analysis level significantly decreased after 1 week of treatment compared with before treatment in the two groups ($P < 0.05$). There was no significant difference between the studied groups regarding complaints before treatment ($P > 0.05$). However, mean changes were significantly decreased after treatment compared with before treatment in the (C) group (84.21%) lower than the (F) group (94.7%) with P value 0.012 and less than 0.001.**

Conclusions: **A single dose of 3 g fosfomycin for the management of lower UTIs was as effective therapeutically and microbiologically as cephalexin for 7 days. Fosfomycin was safe with little side effects. An essential alternative for the frontline empirical therapy of uncomplicated lower UTIs is single-dose fosfomycin-trometamol.**

Keywords: Cephalexin, Fosfomycin, Urinary tract infection

1. Introduction

Urinary tract infection (UTI) is considered the most typical bacterial infections that complicate pregnancy. Although asymptomatic bacteriuria is the most frequent kind, symptomatic infections can also induce pyelonephritis or cystitis. The natural perineal flora contains organisms that can cause urinary infections, most often *Escherichia coli* strains.[1] The American College of Obstetricians and Gynecologists (2002) recommended standard testing for bacteriuria at the initial prenatal appointment due to the fact that the prevalence of UTI during pregnancy is ~8%.[2] The development of bacteriuria from asymptomatic to symptomatic is accelerated during pregnancy and may result in pyelonephritis and unfavorable obstetric outcomes. Researchers have recommended regular culture screening for all pregnant women visiting prenatal clinics due to the harmful consequences of undetected asymptomatic bacteriuria on the mother and the child.[3] *E. coli*, which is responsible for more than 80% of cases, is the more commonly known pathogen in women's uncomplicated UTIs. Of the cases, 15% have *Staphylococcus*

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saprophyticus.[4] Only in cases of symptomatic UTI is empirical therapy advised. The choice of antibiotics for the eradication of ASB should be guided by culture and sensitivity tests.[5] The antibiotic fosfomycin involves a broad-spectrum antibacterial action and exhibits strong in-vitro activity against Gram-negative pathogens in addition to Gram-positive pathogens typically identified in UTIs.[6] Fosfomycin was linked to susceptibility values of 97.2–100% against *E. coli*.[7] Fosfomycin is licensed in a large number of nations throughout the world, including the United States and several European nations, primarily for the treatment of uncomplicated UTIs.[8] Cephalexin works as a bactericidal against some Gram-positive bacteria in addition to other Gram-negative bacteria by preventing the development of the bacterial cell wall. A first-generation cephalosporin antibiotic, cephalexin is a beta-lactam antibiotic. Cephalexin may be taken orally and shares the same mechanism of action as other medications in this family, such as intravenous cefazolin 9.

This study aimed to compare between cephalexin and fosfomycin in the treatment of UTI during pregnancy.

2. Patients and methods

This randomized controlled study was performed on 200 women who attended the Obstetrics and Gynecology Department in Shebin El-Kom Teaching Hospital from October 2021 through April 2022.

2.1. Inclusion criteria

Pregnant women, aged 18–40 years with uncomplicated lower UTIs and gestational age of 14–36 weeks.

2.2. Exclusion criteria

Exclusion criteria were history of allergy to fosfomycin or cephalexin, unable to receive oral medications, irritable bowel syndrome, severe diarrhea, current antibiotic therapy or within the last 72 h, known anatomic urinary abnormality, fever, pyelonephritis and renal failure, leuckopenia and immunosuppressive therapy, elevated liver enzymes, epilepsy and susceptibility results showing resistance to fosfomycin or cephalexin.

2.3. Ethical approval

Patients who decided to participate provided their signed informed permission after being told of the trial's advantages and risks and after receiving approval from the local ethics committee. The trial was registered with the local ethics committee of the Al-Azhar University, Faculty of Medicine, and the study reporting complies with the CONSORT criteria.

All included patients undergone a complete history taking, general and abdominal examination, ultrasound for pregnancy and urinary tract assessment, laboratory tests including complete urine analysis, urine culture test, complete blood count, renal function tests, and hepatic function tests.

2.4. Sample size calculation

Based on previous research Dawood *et al.*[10] reported that complete relief (100%) of symptoms was noticed in the fosfomycin class while improvement of symptoms after 5-day treatment was noticed in 86.49% in cephalexin class ($P = 0.030$). The minimum sample needed was 200 patients; according to the following formula:

$$p = \frac{p_1 + rp_2}{1+r} \quad n \geq \frac{\left[Z_{1-\alpha/2}\sqrt{(r+1)p(1-p)} + Z_{1-\beta}\sqrt{rp_1(1-p_1)+p_2(1-p_2)}\right]^2}{r(p_2-p_1)^2}$$

where n: sample size.

$z1$-α: Z score for CI 95% and equals 1.96.

$z1$-β: Z score for the power of the study is 80% and equals to 0.84.

The proportion of symptomatic improvement in the fosfomycin class (P1): 1.

The proportion of symptomatic improvement in cephalexin class (P2): 0.8649.

The eligible women were allocated into two equal groups:

(F) group: 100 pregnant women with uncomplicated lower UTI, who received one sachet of 3 g fosfomycin tromethamine (Monuril) in 150 ml water on an empty stomach after the evacuation of the bladder at bedtime orally.

(C) group: 100 pregnant women with uncomplicated lower UTI, who received 1 gm cephalexin (Keflex) twice daily orally for 7 days.

2.5. Sample selection and clarification

Midstream urine samples were assembled from the 200 gravidas selected for this study. These urine samples were collected in sterile cups for routine urine analysis and bacteriological quantitative culture and sensitivity according to standard practice, which were made available in outpatient clinic rooms at all times. At 1 week after initiation of treatment, a second midstream urine samples was collected in sterile cups for repeated urine analysis in addition to urine culture. In all groups, there were positive cases that had another course of the antibiotic and all were followed 1 week later with urine analysis and culture.

2.6. Outcome measures

Comparison between two studied groups in cure of patients after the first and second courses of therapy.

2.7. Evaluation of efficiency and safety

Clinical effectiveness, microbiological efficiency, and safety were evaluated on day 14.

2.8. Evaluation of clinical efficiency

Participants' lower UTI symptoms and signs were classified using the following three categories: cured, improved, and ineffective. The terms 'cured' and 'improved' were both used to define 'effective' outcomes to calculating the clinical effectiveness rate.

2.9. Follow up plan

Assessment of pus cells in urine analysis after 1 week of treatment.

2.10. The outcome of the study

2.10.1. Primary

Determination of the changes of pus cells in urine analysis before and after 1 week of treatment.

2.10.2. Secondary

Assessment of the presence of associated symptoms and complications, assessment of side effects of the drugs, and assessment of the cost of the drugs.

2.11. Statistical analysis

To tabulate and statistically analyze the results, SPSS V.25, and Microsoft Excel 2019 were used. Descriptive statistics included mean, median, and SD, while analytical statistics included standard Student's *t*-test: used for comparison between two groups as regards normally distributed (parametric) quantitative data. χ^2: it is used to compare two groups or more regarding one qualitative variable. Multinomial logistic regression: it is used to describe nominal result variables, in which the log chances of the outcomes are modeled as a linear combination of predictor variables. Spearman correlation test (Spearman test): used to show the correlation between two continuous non-normally distributed variables. *P* value less than or equal to 0.05 was considered statistically indicative.

3. Results

(Table 1) A total of 200 pregnant women with uncomplicated lower UTI were included in this study, Their age, gestational age, BMI, parity, and previous mode of delivery did not show any significant differences between groups ($P > 0.05$).

(Table 2) Regarding pus cells in urine analysis before and after treatment did not notice any significant difference between the studied groups ($P > 0.05$). However, pus cells in urine analysis level was indicatively decreased after 1 week of treatment

Table 1. Groups' demography.

Variables	(F) group	(C) group	Total	*t*	*P* value
Age (years)					
Mean ± SD	28.28 ± 6.75	25.65 ± 6.19	26.97 ± 6.59	1.87	0.087
Range	18.00–40.00	18.00–38.00	18.00–40.00		
Median (IQR)	28 (13.5)	25 (10)	25 (12)		
Gestational age (weeks)					
Mean ± SD	23.61 ± 7.61	23.57 ± 6.42	23.59 ± 7.02	0.04	0.968
Range	13.00–35.00	13.00–35.00	13.00–35.00		
Median (IQR)	20.5 (16)	22 (12)	22 (13.5)		

(*continued on next page*)

Table 1. (continued)

Variables	(F) group	(C) group	Total	*t*	*P* value
BMI					
Mean ± SD	29.3 ± 3.6	27.8 ± 4.27	28.55 ± 3.93	1.05	0.67
Range	24–35	22–34	22–35		
Parity	*n* (%)	*n* (%)	*n* (%)	χ^2	
Prime PG	10 (10.00)	24 (24.00)	34 (17.0)	2.11	0.086
Multipara	90 (90.00)	76 (76.00)	166 (83.0)		
Previous mode of delivery					
Cesarean section					
Mean ± SD	1.13 ± 0.96	1.24 ± 1.08	1.19 ± 1.02	0.76	0.448
Range	0.00–3.00	0.00–3.00	0.00–3.00		
Median (IQR)	1.00 (2.00)	1.00 (2.00)	1.00 (2.00)		
NVD					
Mean ± SD	0.84 ± 1.38	0.67 ± 0.32	0.56 ± 1.09	1.81	0.292
Range	0.00–4.00	0.00–2.00	0.00–4.00		
Median (IQR)	0.00 (1.00)	0.00	0.00 (1.00)		

NVD, normal vaginal delivery; *t*, independent *t*-test; χ^2, χ^2 test.

Table 2. Pus cells in urine analysis before and after treatment.

Variables	(F) group	(C) group	Total	*t*	*P* value
Pus cells before treatment					
Mean ± SD	32.50 ± 27.88	28.09 ± 24.73	30.30 ± 26.38	1.18	0.238
Range	6.00–115.00	4.00–111.0	4.00–115.00		
Median (IQR)	19.0 (28.50)	19.0 (21.50)	19.0 (24.00)		
Pus cells after treatment					
Mean ± SD	7.42 ± 10.90	7.21 ± 12.73	7.32 ± 11.82	0.13	0.900
Range	2.00–50.00	1.00–64.00	1.00–64.00		
Median (IQR)	4.00 (3.00)	4.00 (3.00)	4.00 (3.00)		
Changes %	77.1%	74.3%			
Paired *t*-test	17.43	11.58			
P value	<0.001*	0.003*			

t, independent *t*-test.

compared with before treatment in both groups ($P < 0.05$).

(Table 3) Regarding patients' complaints, asymptomatic bacteriuria was found in seven people in the (F) group and five people in the (C) group, while 93% in addition to 95% of patients in the (F) group and (C) group were complaining of cystitis, respectively. Patient's complaints did not notice any significant difference between groups ($P = 0.082$).

(Table 4) Sensitivity of monurol and keflex, side effects, and relief symptoms among the groups did not notice any significant difference.

(Table 5) Complaints before and after treatment showed no statistically significant difference between the two groups regarding complaints before treatment ($P > 0.05$), while the mean changes were indicatively decreased after treatment compared with before treatment in the C group (84.21%) lower

Table 3. Patients' complaints.

Patients' complaints	(F) group [*n* (%)]	(C) group [*n* (%)]	Total [*n* (%)]	χ^2	*P* value
Asymptomatic bacteriuria					
Yes	7 (7.00)	5 (5.00)	12 (6.00)	1.67	0.082
No	93 (93.00)	95 (95.00)	188 (94.00)		
Complaints of cystitis					
Yes	93 (93.00)	95 (95.00)	188 (94.00)	1.67	0.082
No	7 (7.00)	5 (5.00)	12 (6.00)		

χ^2, χ^2 test.

Table 4. Sensitivity of monurol and keflex, side effects and relief symptoms.

Variables	(F) group [*n* (%)]	(C) group [*n* (%)]	Total [*n* (%)]	χ^2	*P* value
Monuril					
Sensitive	97 (97.00)	96 (96.00)	194 (97.00)	0.15	0.893
Resistant	3 (3.00)	4 (4.00)	6 (3.00)		
Keflex					
Sensitive	95 (95.00)	95 (95.00)	190 (95.00)	0.00	1.00
Resistant	5 (95.00)	5 (95.00)	10 (5.00)		
Side effects					
No	97 (97.00)	97 (97.00)	194 (97.0)	1.160	0.740
Vaginal itching	2 (2.0)	0 (0.00)	2 (1.00)		
GIT upset	1 (1.0)	3 (3.0)	4 (2.00)		
Relief symptoms					
Positive	88 (94.62)	80 (84.21)	168 (89.36)	0.272	0.602
Negative	5 (5.38)	15 (15.79)	20 (10.64)		

t, Student's *t*-test; χ^2, χ^2 test.
*Indicative.

Table 5. Complain before and after treatment.

Variables	F group [*n* (%)]	C group [*n* (%)]	Total [*n* (%)]	χ^2	*P* value
Complaints before treatment					
Positive	93 (93.00)	95 (95.00)	188 (94.00)	1.67	0.082
Negative	7 (7.00)	5 (5.00)	12 (6.00)		
	(F) group	(C) group			
Complaints after treatment					
Negative	88 (94.62)	80 (84.21)	168 (89.36)	4.18	0.035*
Positive	5 (5.38)	15 (15.79)	20 (10.64)		
Changes (%)	94.7	84.21			
χ^2 test	10.16	6.190			
P value	<0.001*	0.012*			

than the F group (94.7%) with a *P* value of 0.012 and less than 0.001, respectively.

4. Discussion

The present study demonstrated that urine analysis before and after treatment did not notice any indicative change between the studied groups ($P > 0.05$). However, pus cells in urine analysis was indicatively decreased after 1 week of treatment compared with before treatment in both groups ($P < 0.05$). However, in another study, there were very statistically indicative differences between the three examined classes in both the first and second cultures.[11] This might be because not all patients had urine cultures taken, either at admission or after treatment, either because the test could not be done or someone lost track of the patient. In addition, Dawood et al.[10] stated that the second urine sample was performed 7 days following the start of therapy, and pus cells in urine analysis (0–11/HPF) were identified in the Fosfomycin class compared with (16–25/HPF) in the Nitrofurantoin class, with a *P* value of 0.002. In the nitrofurantoin class, compliance was 34/37 (91.89%), but in the fosfomycin class, it was 38/38 (100%) ($P = 0.001$). The frequent causes of insufficient compliance were multiple doses in addition to adverse effects.[10]

According to the results of this study, it showed no indicative change between two groups in terms of keflex and monurol sensitivity ($P > 0.05$). Bader et al.[12] have shown that fosfomycin is more effective than other antibiotics and less likely to cause bacterial resistance.[12] One (2.63%) case of persistent infection was recorded in the fosfomycin group, whereas roughly eight (21.62%) instances were identified in the nitrofurantoin class.[10]

Fosfomycin was found to be effective in vitro against the majority of strains and types of identified bacteria.[13]

Furthermore, it is categorized by the FDA as a pregnancy category B medicine, indicating that it is quite safe to use during pregnancy. In this Maternal Infection Screening and Treatment study, the patterns of uropathogens' antimicrobial susceptibility were illustrated. A modest 62% of individuals were susceptible to cephalexin (kefalex).[14]

In this study, asymptomatic bacteriuria was found in seven patients in the group that received fosfomycin and five patients in the group that received cephalexin, whereas 93 and 95% of patients in the (F) group and the (C) group complained of cystitis,

respectively. Therefore, you cannot find any indicative change in patient complaints between analyzed groups ($P = 0.082$). Other findings were reported by Ceran et al.[15] as gastric complaints were noted in three (3.9%) of 77 patients using fosfomycin and two (3.07%) of 65 patients using ciprofloxacin.[15]

The current study found that there was no significant change in the side effects between the two groups ($P = 0.74$). However, according to El-Mehy *et al.*[11] there was a significant change between the fosfomycin, nitrofurantoin, and cephalosporin classes substantially in terms of adverse effects reported: seven instances in fosfomycin class, 13 in nitrofurantoin class, and 14 in cephalosporin class.[11] Despite similar levels of tolerance in each of the three research groups, the safety mode of fosfomycin was more tolerable than that of the other two groups (19.9 vs. 36.9% and 39.9%). In their study, GIT upset was the most frequent adverse effect. In the study by Iarikov et al.[16] the most frequent side effects in the group that used fosfomycin were nausea and vomiting.[16] Furthermore, there was an indicative change in the reported adverse effects between the group that used nitrofurantoin (35.14%), in addition to the group that used fosfomycin (seven instances, 18.42%), with a P value of 0.003, indicating that the reported side effects were indicatively different. Fosfomycin's most frequent adverse effects were dizziness (5/38; 13.16%), nausea/vomiting (5/38; 28.95%), and diarrhea (11/38; 13.16%).[10] This was similar to other studies by Mody and Juthani-Mehta[17] and Sastry et al.[18]

As a result of the patient group's lack of regular follow-up and their perception of minor symptoms as not serious enough to report, the low rate of adverse effects in the current research was thought to be a reflection of the fact that the patient group was not monitored closely.

4.1. Conclusion

A single dose of 3 g fosfomycin for the management of lower UTIs was as effective clinically and microbiologically as cephalexin for 7 days. Fosfomycin was safe with little side effects. An essential alternative for the frontline empirical therapy of uncomplicated lower UTIs is single-dose fosfomycin trometamol.

4.2. Limitations of the study

The methodologies, tools, and procedures used to acquire the data, the restricted availability of the data, and the time constraints might all be potential limitations in this study.

Conflicts of interest

There are no conflicts of interest.

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