

## Efficacy and Safety of Fosfomycin Single-Dose Therapy Compared to Nitrofurantoin and Cephalosporin in Pregnant Women with Lower Urinary Tract Infection: A Randomized Controlled Trial

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### ABSTRACT

**Background:** Fosfomycin is a bactericidal drug that inhibits bacterial cell wall and also reduces the adherence ability of bacteria to uro-epithelial cells with a broad anti-bacterial activity against both Gram-negative and Gram-positive.

**Objective:** To compare the efficacy and safety of fosfomycin compared to nitrofurantoin and cephalosporin in pregnant women presented with lower urinary tract infection. **Patients and Methods:** This was a double blinded, randomized controlled trial conducted at Shebin El-Kom Teaching Hospital from Aug 2019 to Aug 2020. Patients experienced uncomplicated lower urinary tract infection either asymptomatic bacteriuria or cystitis were recruited. Patients were randomly allocated via a random table number into three groups, each group comprised 35 patients. Group I received 3 g oral fosfomycin weekly, group II received 100 mg oral nitrofurantoin three times daily, and group III received 500 mg oral cephalosporin three times daily. After 7 days of treatment, all studied groups were subjected to urine sampling and culture analysis and were examined for occurrence of side effects. **Results:** All patients enrolled in our study had uncomplicated lower urinary tract infection either cystitis (n=85 cases) or asymptomatic bacteriuria (n=20 cases). There was clinical difference in urine pus cells and urine culture in fosfomycin after treatment compared to other groups. The side effects were reported in 7 cases with fosfomycin compared to 14 in other two groups with significant difference.

**Conclusion:** Fosfomycin tromethamine was proved to be more effective, safe, and fewer side effects were reported, which makes fosfomycin the drug of choice for uncomplicated lower urinary tract infection during pregnancy.

**Keywords:** Asymptomatic Bacteriuria, Cephalosporin, Cystitis, Fosfomycin, Nitrofurantoin, Pregnancy, UTIs.

### INTRODUCTION

Urinary tract infections (UTIs) are common bacterial infections among pregnant women as it has been reported that about half of women will catch at least one of the UTIs during their life time and also about 25% of them will experience recurrence <sup>(1)</sup>. Uncomplicated lower urinary tract infection (uUTI) and asymptomatic bacteriuria (ASB) are reported to be the main common types of UTIs in women in which the uUTI is often pointed to acute cystitis characterized by symptoms such as dysuria, hematuria, and/or suprapubic pain which requires a course of antibiotic therapy. Moreover, ASB is self-limiting and doesn't require antibiotic therapy in most cases except in pregnancy <sup>(2)</sup>.

Current guidelines recommend an early use of antibiotics as main treatments of UTIs <sup>(3, 4)</sup>, despite the frequent use of antibiotic usually leads to bacterial resistance, which exacerbates the resistant pathogens either multidrug-resistant (MDR) or extensive drug resistant (XDR), which causes more complicated UTIs <sup>(5)</sup>. This resistance has affected our management towards such disease which had led us to modify the disease antibiotic protocol <sup>(6)</sup>. Fosfomycin trometamol (Monurol<sup>®</sup>) was approved from FDA as category B for the treatment of uncomplicated lower urinary tract infections (UTIs). However, it has a good antibiotic activity against Gram-positive and Gram-negative bacteria, the exact mechanism for its broad activity is not well-understood; but it was

suggested that fosfomycin inhibits the synthesis of peptidoglycan earlier than  $\beta$ -lactams and glycopeptides <sup>(7, 8)</sup>. Fosfomycin is usually given as a single dose of 3 g weekly which can result in good tolerance. Moreover, the common side effects that has been reported from taking fosfomycin in other clinical trials were mainly affecting the GIT such as diarrhea, nausea, or vaginitis <sup>(8, 9)</sup>. Many research on randomized controlled trials showed that fosfomycin single dose had similar efficacy to 3-7 days of other antibiotic regimens such as cephalosporin, cotrimoxazole, or nitrofurantoin in uncomplicated UTI <sup>(8-10)</sup>. In our study, we compared the efficacy and safety measures of single dose 3 g fosfomycin given orally versus 100 mg nitrofurantoin given orally three times daily and 500 mg cephalosporin given also three times daily in non-complicated lower urinary tract infection in pregnant women at Menoufia University Hospital.

### PATIENTS AND METHODS

This was a prospective, double blinded, and randomized controlled trial conducted at the Department of Obstetrics and Gynecology at Shebin El-Kom Teaching Hospital from August 2019 till August 2020.

One hundred and five pregnant women between 12 and 36 gestational age were enrolled in our study according to the following inclusion criteria: Patients with uncomplicated lower UTIs either asymptomatic or cystitis,

while the exclusion criteria were: a) History to allergy to fosfomicin; b) Irritable bowel syndrome; c) Diabetes or immune-compromised patients; d) History of congenital anatomic urinary anomalies.

Our sample size was calculated using Epi info 0.7 programs with two-sided confidence level of 95% with power of study with 80%; the Z score for 95% CI equaled 1.96 and 0.84 for the power of the study. The estimated sample size were 106 patients, but we were able to obtain only 105 patients. Patients were randomly allocated into three groups, where the randomization process was generated using a random number table. And the allocation system was done using opaque closed envelopes by 1:1:1 ratio in which each envelope contained one assignment for each patient.

**Group I (n= 35 cases):** received a single dose of 3 g fosfomicin orally weekly.

**Group II (n= 35 cases):** received 100 mg nitrofurantoin three times daily orally for 7 days.

**Group III (n=35 cases):** received 500 mg cephalosporin three times daily for 7 days.

The fosfomicin patients group were advised to take the fosfomicin dose by dissolving it into half cup of water, then take it before bedtime. Also, they were advised to empty their bladder before taking the fosfomicin dose, while other groups were given the prescribed dose in capsule form. Not any of the participant nor the authors were aware of the allocation system as well as which intervention patients have taken.

**Ethical approval:**

A written consent was obtained from patients after explanation of the study and **ethical approval was obtained from Menoufia University Ethical Committee.**

All included patients were subjected at the beginning of the study to:

**A) Detailed clinical history** including age, parity, gestational age, any presenting symptoms, menstrual history such as first day of last menstrual period (LMP) and expected date of delivery (EDD).

**B) Full clinical examination** including general examination such as measurement of blood pressure, pulse, temperature, and presence of edema, and abdominal examination such as fundal level, organomegaly, and renal angle tenderness.

**C) Investigation** including ultrasound for pregnancy an urinary track assessment, and laboratory tests as complete urine analysis and urine culture test. After 7 days of the trial, a questionnaire for relief of symptoms, compliance, or any complications was taking from all patients.

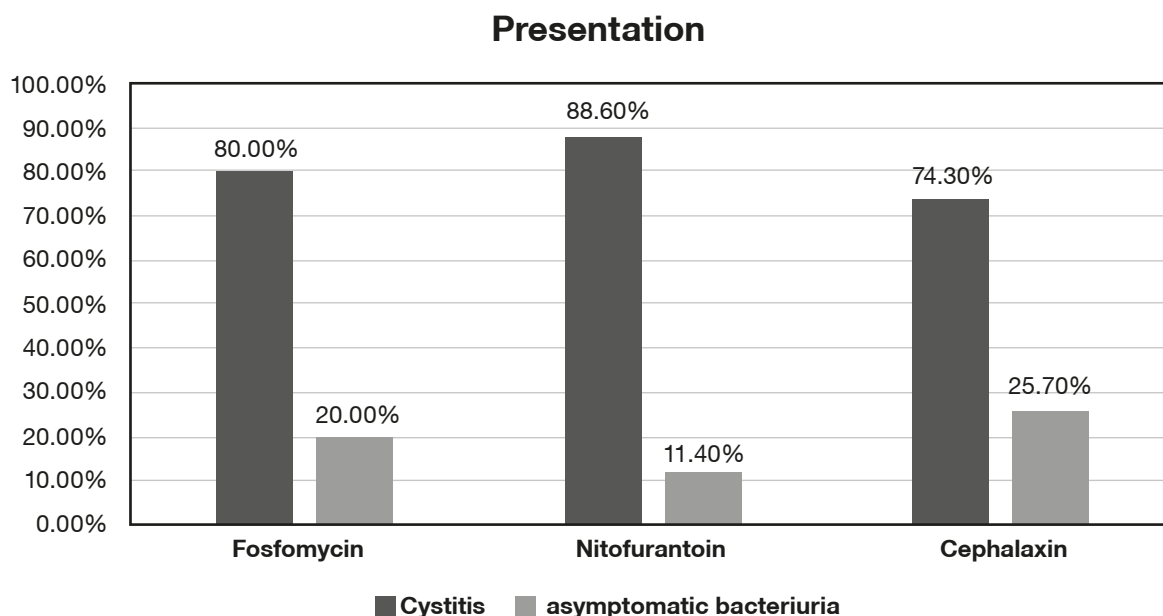
The designed questionnaire set by authors' collaboration was made of two major sections: first section comprised the demographics data about patients, second section considered the efficacy of the treatment along with any reported side effect of the drug taken.

**Statistical Analysis**

Data were analyzed using SPSS version 25, USA. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation). ANOVA test comparison. P-value < 0.05 was considered to be significant.

**RESULTS**

All patients have reported either cystitis (n= 85 cases) or asymptomatic bacteriuria (n= 20 cases). No patients were excluded from our study as shown in (Figure 1).



**Figure (1): distribution of cystitis and asymptomatic bacteriuria among the three studied groups.**

There was no significant difference between all groups according to the demographics data (Table 1).

**Table (1):** Demographic data of the three studied groups

Comparison	Fosfomycin N=35	Nitrofurantoin N=35	Cephalexin N=35	tatistical test	P value
Age (years) Mean $\pm$ SD	27.09 $\pm$ 7.3	25.91 $\pm$ 3.09	25.89 $\pm$ 4.74	F test 0.581	0.561
Gravidity Mean $\pm$ SD	2.20 $\pm$ 1.11	1.80 $\pm$ 0.98	1.83 $\pm$ 1.2	F test 1.829	0.166
Parity Mean $\pm$ SD	1.40 $\pm$ 0.81	1.22 $\pm$ 0.81	1.5 $\pm$ 0.81	F test 1.011	0.367
Gestational age (weeks) Mean $\pm$ SD	23.91 $\pm$ 4.1	24.3 $\pm$ 3.4	23.11 $\pm$ 3.12	F test 0.014	0.366
Cystitis (n, %)	28 (80%)	31 (88.6%)	26 (74.3%)	X <sup>2</sup> 2.347	0.309
Asymptomatic Bacteriuria (n, %)	7 (20%)	4 (11.4%)	9 (25.7%)		

There were highly statistically significant differences between the three studied groups as regard pus cells and cure rate (Table 2).

**Table (2):** Analysis of urine samples taken among the three studied groups

Urine analysis		Fosfomycin		Nitrofurantoin		Cephalexin		P value
		No	%	No	%	No	%	
Urine analysis 1 (at admission)	(10-40) pus cells/HPF	15	42.9%	29	82.9%	26	74.3%	27.4 <0.001*
	(50-80) pus cells/ HPF	9	25.7%	6	17.1%	9	25.7%	
	(over 100) pus cells/HPF	11	31.4%	0	0.0%	0	0.0%	
Urine analysis 2 (after 7 days of treatment)	(0-10) pus cells/ HPF	34	97.1%	28	80%	26	74.3	7.3 0.026*
	(15-20) pus cells/ HPF	1	2.9%	7	20%	9	25.7	
Cure rate		34	97.1%	30	85.7%	27	77.1%	6.099 0.047*

\*significant

Urine culture samples weren't done for all patients neither at admission nor after the 7 days of treatment due to inability to perform the test or lost follow up in which at admission there were 12 patients missing in fosfomycin group, 14 missing in nitrofurantoin group, and 6 missing in cephalosporin group.

There were highly statistically significant differences between the three studied groups in both the first and second culture regardless the lost follow up (Table 3).

**Table (3):** Analysis of urine culture samples taken among the three studied groups

Urine Culture		Fosfomicin		Nitrofurantoin		Cephalexin		P value
		N	%	N	%	N	%	
Urine Culture 1 (at admission)	<100000 CFU/ml	9	39.1%	3	21.4%	3	10.3%	28.6
	>100000 CFU/ml	14	60.90	0	0%	12	41.4%	
	no growth	0	0.0	11	78.6	14	48.3%	
Urine Culture 2 (after 7 days of treatment)	10000 CFU/ml	8	32.0	0	0%	0	0%	14.17
	30000 CFU/ml	0	0.0	0	0%	3	25%	
	no growth	17	68.0	6	100%	9	75%	

\*significant

The side effects were recorded in only 7 cases in fosfomicin group compared to 13 in nitrofurantoin group, and 14 in cephalosporin group with significant difference between the three groups (Table 4).

**Table (4):** Safety and side effects of drug among the studied groups

Compare	Fosfomicin		Nitrofurantoin		Cephalexin		X <sup>2</sup>	P value
	N	%	N	%	N	%		
Side effects of drug	7	20%	13	37.1%	14	40%	3.741	0.154
Diarrhea	3	42.8%	6	46.2%	7	50%	1.423	0.999
Nausea/vomiting	5	70.4%	10	76.9%	9	64.2%		
Vaginitis	2	28.5%	5	38.4%	6	42.8%		
Dizziness	4	57%	7	53.8%	8	57.1%		
Headache	3	42.8%	5	38.4%	6	42.8%		
Dyspepsia	5	70.4%	8	61.5%	7	50%		

## DISCUSSION

Urinary tract infections (UTIs) are prominent among pregnant women due to the physiological changes that occur during pregnancy, which favor the UTIs occurrence. UTIs may vary from asymptomatic bacteriuria, pyelonephritis with systematic pictures, or cystitis<sup>(11, 12)</sup>. Asymptomatic bacteriuria doesn't usually require antibiotic therapy except in pregnancy, as it can be changed into symptomatic bacteriuria as cystitis or pyelonephritis<sup>(13)</sup>. The repeated courses of different antibiotics aligned with repeated lower urinary tract infections resulted in highly bacterial resistant to most of antibiotics used which requires shifting to treat the UTIs in pregnant women as early as possible so we can increase the health as well as the decrease in progressive UTIs during pregnancy<sup>(14, 15)</sup>.

Fosfomicin, nitrofurantoin along with cephalosporin are considered to be first line treatment in non-complicated form of UTI in pregnant females<sup>(16)</sup>. Although nitrofurantoin is a category B drug prescribed

in pregnancy, there are a lot of concerns about its efficacy, safety, or patient compliance. Moreover, it's not prescribed to pregnant women who are in near term or during delivery as it can cause hemolytic anemia<sup>(17, 18)</sup>. On the other hand, fosfomicin trometamol is considered also category B used often in a single dosage form, but it was approved to have higher efficacy and lower rate of being a bacterial-resistant drug when compared to other antibiotics such as quinolones, cephalosporin even if it's given as a single dose of 3 g; making it the first drug of choice in treatment for uncomplicated UTIs<sup>(19, 20)</sup>.

Many studied that mentioned the efficacy and safety of fosfomicin compared to other drugs to treat uncomplicated UTIs in pregnancy showed that fosfomicin proved to have higher efficacy, higher improvement rate, and also better patient compliance<sup>(21-23)</sup>.

A study by Usta *et al.*<sup>(24)</sup> compared fosfomicin single dose of 3 g orally to amoxicillin-clavulanic, and cefuroxime axetil in 324 pregnant women presented with

lower urinary tract infection. The results of the three groups didn't differ in demographics, cure rate, adverse effects, or clinical success rate; but there was an observed better compliance in fosfomicin group than other 2 groups (p-value <0.05) suggesting that treatment of UTIs with single dose of fosfomicin trometamol owing to its simpler use is as effective as other drugs used in the study.

Another study by **Dawood *et al.*** <sup>(25)</sup> reported one case (2.63%) with persistent infection in fosfomicin group and about 8 (21.62%) cases were reported in nitrofurantoin group. Also, similar fosfomicin resistance of 0%-2.2% were reported by **Pullukçu *et al.*** <sup>(26)</sup> and **Ko *et al.*** <sup>(27)</sup>. Our study showed (97.1%) cure rate in fosfomicin group, which was better than other 2 groups, however **Ceran *et al.*** <sup>(28)</sup> reported comparable results when compared fosfomicin with ciprofloxacin along with disappearance of side effects in about 80% of the cases. This can be attributed to the low usage rate of fosfomicin in our locality giving it less occurrence of bacterial resistance.

In our study, although the tolerance was comparable in all three studied groups, safety profile of fosfomicin was more acceptable than other 2 groups 20% vs 37.1% and 40%. Nausea and vomiting were the most common side effect reported by our study, and this comes align with another study by **Iarikov *et al.*** <sup>(29)</sup> who reported that nausea and vomiting were the common side effects that occur in fosfomicin group. **Dawood *et al.*** <sup>(25)</sup> reported that diarrhea was the commonest complication in fosfomicin group along with other studies that mentioned the same side effect in fosfomicin group <sup>(28, 30-32)</sup>.

## CONCLUSION

We recommend fosfomicin trometamol to be the drug of choice as regard uncomplicated UTI during pregnancy based on its higher efficacy, safety, low resistance, and fewer reported side effects compared to other antibiotic regimens.

## Registry:

This randomized controlled trial (RCT) was approved by Egyptian Universities Libraries Consortium (EULC) with code 9114481.

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