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Gastrointestinal complications after fosfomycin in pregnant women

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Summary

Background. Urinary tract infections (UTIs) are one of the leading infections in pregnant women, associated with, among others, urinary stasis and glycosuria during pregnancy. The most common uropathogen is *Escherichia coli* (uropathogenic Escherichia coli, UPEC). The consequences of long-term UTIs in pregnancy include premature birth and weight reduction of the child. Therefore, it is essential to implement effective antibiotic therapy and repeat urine culture 7–14 days after the end of treatment. Antibiotic therapy of UTIs in pregnancy is applied regardless of clinical symptoms. Fosfomycin is an antibiotic with putative activity against several bacteria, used for treating urinary tract infections and asymptomatic bacteriuria. ***Material and methods.*** We describe a case report of a 28-year-old pregnant patient with a urinary tract infection who experienced a gastrointestinal adverse reaction in the form of diarrhea and nausea following the treatment with fosfomycin. ***Results.*** The symptoms resolved within three days. ***Conclusions.*** The described case confirms the risk of gastrointestinal complications following the administration of fosfomycin. *(Farm Współ 2023; 16: 43-48) doi: 10.53139/FW.20231605*

Keywords: Fosfomycin, pregnancy, urinary tract infections in pregnancy, asymptomatic bacteriuria, adverse drug reactions

Introduction

Urinary tract infections (UTIs) are considered one of the most common medical conditions complicating pregnancy, diagnosed in as many as 20–60% of all gestations [1-3]. A urinary tract infection is diagnosed when bacteria overgrowth is observed in the urinary tract (≥105 counts/mL of urine), irrespective of the presence of clinical symptoms [2]. UTIs are commonly caused by ascending movement of bacteria that colonize the lower gastrointestinal and genitourinary tract [4]. In pregnancy, UTIs can be caused by the same uropathogens which commonly cause them in non-pregnant individuals. Commonly isolated bacteria include *Escherichia coli* (responsible for 80–90% of cases), *Klebsiella pneumoniae*, *Staphylococcus saprophyticus, Staphylococcus aureus,* Group B *Streptococcus* (GBS), *Pseudomonas aeruginosa, Proteus mirabilis, Acinetobacter* [2,3]. These uropathogens have proteins on the cell surface that enhance bacterial adhesion leading to increased virulence [5]. Pregnant women are predisposed to urinary tract infections due to immunologic and physiologic changes of the urinary tract. Early in pregnancy, around seven weeks, physiological changes of the urinary tract occur due to the relaxation of smooth muscles associated with progesterone. Later, with a peak at 22–26 weeks, the compression of the ureter by the gravid uterus leads to dilation of the ureter (which may be marked). Moreover, the phenomenon of maternal ureterohydronephrosis (UHN)- one of the most common anatomical changes during pregnancy (occurs in 43-100% of pregnant women) is aggravated. Frequent urination usually occurs due to a decrease in bladder capacity. These factors contribute to urinary stasis, and vesicoureteral reflux may also be observed. Apart from that, differences in pH and osmolality of the urine, as well as pregnancy-induced glycosuria and aminoaciduria further open doors for bacterial growth and UTI. Pregnancy is a state of relative immunocompromise, which may be another cause for the increased frequency of UTIs [5-7]. Furthermore, urinary catheterization, frequently performed during labor, may introduce pathogens leading to urinary tract

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infections. Changes in bladder sensitivity and overdistention in the postpartum period may also predispose to UTI [5]. The most significant factor predisposing to urinary tract infections during pregnancy is asymptomatic bacteriuria (ASB), defined as more than 100,000 organisms/mL on a clean catch urinalysis (obtained from an asymptomatic patient). ASB affects 2-10% of pregnant women [1,3]. UTIs can be classified as lower urinary tract infections, including both asymptomatic bacteriuria (ASB) or acute cystitis (AC) and upper urinary tract infections or acute pyelonephritis (APN) [3]. According to review articles, the prevalence of the above-mentioned ailments in pregnancy is as follows: 2–10% for asymptomatic bacteriuria, 1–4% for cystitis, and 1–2% for pyelonephritis [4]. Pregnant women are recommended to be screened for ASB at the first prenatal visit (most often performed with a clean catch urine culture) [5]. The etiology of UTI in pregnancy is not entirely understood. Nevertheless, individuals at high risk for UTI include those suffering from diabetes, polycystic kidney disease, sickle cell disease, urinary tract abnormalities, previous history of UTI, and immunodeficiency. Apart from that, maternal age, race, socioeconomic status, and parity might be associated with UTI in pregnancy [2,4]. In pregnant women, untreated ASB can turn into symptomatic AC in 30% of patients and may progress to APN in up to 50% of those patients, which have been associated with several complications for both the mother and the unborn child [3]. Pyelonephritis is the most common serious medical condition seen in pregnancy (and one of the most common causes of maternal sepsis, the third leading cause of maternal mortality worldwide), complicating 0.5% of pregnancies [5,8]. It is more often right-sided; however, it may be bilateral in up to 25% of cases [5]. APN in pregnancy can lead to preterm labor, low birth weight, anemia, septicemia, respiratory insufficiency, and, exceptionally, maternal death. Preeclampsia and birth defects have also been associated with UTIs in pregnancy [1-2,4]. There were reports from the clinical trials in the 1960s and 1970s that untreated ASB had a 20 to 30% risk of progressing into pyelonephritis and that early diagnosis and adequate treatment helped reduce the risk by 80% [2]. However, recent studies show no good-quality evidence for an association between ASB and acute pyelonephritis if ASB is untreated. The evidence that the treatment of ASB results in a reduction in the incidence of low birth weight and preterm birth is low-to-moderate–quality. Thus, the screening practices for ASB with only a single urine culture are justified in the first trimester [1]. Clinical guidelines recommend prescribing a short course of antibiotics if bacteriuria is found. About two-thirds of women with a UTI in pregnancy take an antibiotic [4]. However, studies on recurrent UTIs during pregnancy are lacking; therefore drawing conclusions regarding prophylactic measures may be troublesome [1]. Preferred antimicrobials for managing pyelonephritis are amoxicillin combined with an aminoglycoside, third-generation cephalosporins, or carbapenems. Nevertheless, almost 20-40% of cases of *E. coli* are resistant to ampicillin and amoxicillin, so their use is not optimal when this bacteria is identified. Fosfomycin is often a useful alternative [1,6].

Case report

The report describes a case of a 28-year-old woman in her first pregnancy. The pregnancy was uneventful, the patient regularly had recommended check-ups, and the test results were typical. In the 27th week of pregnancy, a control urine test was performed - *E. coli* was detected in an appropriately collected urine sample. Since the patient reported an adverse effect (allergic reaction) after the treatment with amoxicillin used before pregnancy, fosfomycin in a single dose of 3 g was recommended to treat the infection. The woman was advised to drink at least 1.5 l of water daily and to maintain personal hygiene (avoiding long and frequent baths in the bathtub). After fosfomycin use, the patient developed gastrointestinal disorders (diarrhea and nausea). The symptoms resolved within three days.

Discussion

Fosfomycin is a bactericidal antibiotic derived from phosphonic acid, first isolated from *Streptomyces spp.* in 1969. It is a low-molecular-weight agent with broad-spectrum bactericidal activity against *staphylococci, enterococci, Haemophilus spp.,* and most enteric Gram-negative bacteria. It also has excellent activity against most *E. coli* strains [9,10]. Fosfomycin is available (in numerous countries for various indications) in two oral formulations, fosfomycin calcium and fosfomycin trometamol (also known as fosfomycin tromethamine - a soluble salt with better bioavailability), and fosfomycin disodium for intravenous use [10,11]. Due to the considerable incidence of multidrug-resistant microorganisms for which fosfomycin constitutes (alone or in combination) a treatment

alternative, the use of this antibiotic has increased notably [12]. Fosfomycin has a single mechanism of action resulting in irreversible inhibition of an early stage in cell wall synthesis (acts on bacteria in the growth phase). This antibiotic is an analog of phosphoenolpyruvate and is characterized by an epoxide ring and a phosphonic group. The drug is introduced to the interior of the bacteria through permeases, such as the glycerol-3-phosphate transporter (GlpT) and glucose-6-phosphate [G6P] transporter (UhpT). Fosfomycin blocks the first step of peptidoglycan synthesis. It binds covalently with the UDP-N-acetylglucosamine-3-0-enolpyruvyl transferase (MurA) enzyme (responsible for catalyzing the formation of N-acetylmuramic acid (precursor of peptidoglycan)) and inhibits the first steps of peptidoglycan synthesis in the bacterial wall, thereby causing lysis of the bacterial cells [12,13]. Because the formation of N-acetylmuramic acid in Gram-positive and Gram-negative bacteria is required for synthesizing peptidoglycan, fosfomycin's spectrum of action is very broad. The discussed antibiotic has considerable activity against *E. coli, Klebsiella and Enterobacter spp., Proteus mirabilis, Shigella spp., Serratia spp., Citrobacter spp.,* and *Salmonella spp.* Moreover, its lack of cross-resistance makes fosfomycin utile for treating infections by multidrug-resistant pathogens such as *Enterococcus spp.* and *Staphylococcus spp.* (including methicillin-resistant *Staphylococcus aureus* (MRSA) but except *Staphylococcus capitis* and *Staphylococcus saprophyticus*, which are inherently fosfomycin-resistant), methicillin-resistant coagulase-negative *staphylococci* (MRCNS), vancomycin-resistant *enterococci* (VRE), penicillin-resistant *Streptococcus pneumoniae,* extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales,* carbapenemase-producing *Enterobacterales* (CPE), multidrug-resistant *Pseudomonas aeruginosa, and also Listeria monocytogenes, Neisseria gonorrhoeae, Aerococcus urinae, and Helicobacter pylori.* Regarding fosfomycin's anaerobicide activity, it is also efficacious against *Peptococcus spp. and Peptostreptococcus spp.* but not against *Bacteroides spp.* Around 81-100% of ESBL-producing *E. coli* strains are still susceptible to fosfomycin [12-14]. Some bacteria are either inherently resistant to fosfomycin *(Morganella morganii)* or considered to be so *(Acinetobacter spp., Stenotrophomonas maltophilia, Burkholderia cepacia and Mycobacterium tuberculosis)* [13]. Fosfomycin is able to penetrate and reach relevant concentrations in inflamed tissues, aqueous and vitreous humor, CNS, soft tissues, bone, lungs, and abscesses. It also actively accesses the interior of polymorphonuclear leukocytes [9,12]. Another feature of his drug is reducing the adherence of bacteria to some epithelia, such as the urinary epithelium. It also performs an immunomodulatory effect by suppressing the production of tubular necrosis factor-β and several interleukins (IL-1β, IL-2, IL-8, etc.), as well as improving the phagocytic activity of neutrophils. It has been shown (on animal models) that fosfomycin acts on biofilms not only by decreasing or eradicating them but can also by modifying their structure as well [13]. Fosfomycin can be used in combination with other antimicrobial agents acting via different mechanisms, allowing for a synergistic effect, reduced dosages, and lower toxicity [12]. Fosfomycin tromethamine is approved as a 3-gram one-time dose for treating urinary tract infections. Its oral bioavailability ranges between 33 and 58%. Absorption occurs in the small intestine. Food may decrease the rate and extent of absorption (37% fasting versus 30% with food), the maximum concentration in serum (C_{max}) may be higher under fasting conditions (12.1 ± 0.6 mg/liter and 7.8 ± 1.6 mg/liter, respectively) [12,15-17]. Age does not seem to affect absorption. Fosfomycin trometamol is involved in enterohepatic circulation. The drug is transported to the tissues, including the kidneys and bladder wall. Fosfomycin does not bind to plasma proteins and crosses the placental barrier [15,16]**.** Fosfomycin's mean serum elimination half-life ($t_{1/2}$) is estimated at 5.7 h; however, it may be prolonged in elderly patients [15]. Mean urine fosfomycin concentrations are above the minimum inhibitory concentration (MIC) level of 128 μg/ml for at least 24 hours after oral administration of a 3 g dose, both in the fasted and fed state; however, the time to reach peak concentration in the urine is delayed by four hours [16]. The drug is excreted nonmetabolized through glomerular filtration - 11 to 60% of the drug can be found in the urine within 24 h following administration depending on age, fasting, and renal function- older age, administration with a meal, and deteriorating renal function results in slower elimination [15]. Although food may decrease the rate of absorption, the total amount of active substance excreted in the urine over time remains the same. It is also excreted to a lesser extent in the feces (18-28% of the dose) [16].

Konwar et al. presented a systematic review and meta-analysis of four studies to evaluate the compara-

tive efficacy and safety of fosfomycin and nitrofurantoin in managing uncomplicated UTI. The analysis included 750 patients in a fosfomycin group and 747 patients in nitrofurantoin groups with uncomplicated UTI (uUTI) and pregnant females with asymptomatic bacteriuria. The analysis did not reveal a significant difference between fosfomycin and nitrofurantoin-treated groups in the proportion of patients who experienced an adverse event [18]. Although fosfomycin is recommended as the first-line treatment in pregnant women, the data about its safety profile in this population are limited. Wang et al. conducted a systematic review and meta-analysis to investigate the efficacy and safety of single-dose fosfomycin tromethamine compared to other antibiotic agents in women suffering from lower uncomplicated UTI and pregnant women with uncomplicated UTI or ASB. The data from 21 studies were analyzed. The results showed that single-dose fosfomycin tromethamine was comparable with other antibiotic agents in clinical resolution of uncomplicated UTI in non-pregnant and pregnant women, moreover there was no difference in overall microbiological resolution among non-pregnant women with uUTI, pregnant women with uUTI and pregnant women with ASB. Also, the incidence of adverse reactions to fosfomycin was scrutinized in this review. Most frequent adverse events were mainly gastrointestinal, but no serious fosfomycin-related adverse events were reported. Fifteen out of twenty-one analyzed studies reported the incidence of adverse events in a total of 3201 participants. No marked differences in adverse events between single-dose fosfomycin and comparator antibiotics were found. The incidence of adverse events across five studies occurred similarly between pregnant individuals treated with single-dose fosfomycin tromethamine and those treated with other antibiotics (577 participants). There was no difference in the occurrence of adverse events for non-pregnant patients treated with single-dose FT in relation to patients treated with other antibiotics across ten studies (2624 patients). The conclusion was that single-dose fosfomycin produced equivalent clinical outcomes to other antibiotics in terms of clinical and microbiological efficacy [19]. Another systematic review and meta-analysis performed by Schulz et al. aimed to assess the microbiologic efficacy of antibiotic therapy in a single dose compared with multiple doses in lower UTIs during pregnancy. This analysis included data from nine randomized controlled studies, where the population was pregnant women (a total of 1063 women were included), a microbiologic cure was attained, and one of the treatment groups received single-dose antibiotic therapy. The analysis yielded that the use of a single-dose antibiotic therapy had statistically similar efficacy (attested by urine culture) to that observed in the group treated for a longer period and can be recommended for lower urinary tract infections during pregnancy, especially using fosfomycin [20]. An observational cohort study by Philipps et al. investigated the teratogenic risk of fosfomycin in human pregnancy. The aim was to assess pregnancy outcomes after first-trimester exposure to this drug by comparing 152 pregnant women exposed to fosfomycin to 456 unexposed pregnancies. Only 1 out of 146 exposed infants was affected by a major birth defect compared to 15 out of 399 in the non-exposed cohort. Spontaneous abortions were observed in 5/152 cases in the fosfomycin cohort, while in the comparison cohort, there were 53/456 cases. Thus, no increased risk of major Congenital Anomalies (CA) after fosfomycin exposure during early pregnancy was observed; however, the sample size was limited [21]. To assess more precisely the risk of major CA after fosfomycin exposure during the first trimester of pregnancy, Benevent et al. performed a comparative study of three groups of pregnant women: exposed at least once to fosfomycin during the first trimester; exposed at least once to nitrofurantoin during the first trimester; and exposed neither to fosfomycin nor to nitrofurantoin in the three months prior to pregnancy or during pregnancy. A total of 2724 (2.0%) pregnant women received at least one fosfomycin prescription during the first trimester, 650 (0.5%) received nitrofurantoin during the first trimester, and 133,502 (97.5%) pregnant women were not exposed to fosfomycin nor to nitrofurantoin. Exposure to fosfomycin during the first trimester of pregnancy was not associated with an increased risk of major CA, compared to first-trimester exposure to nitrofurantoin (2.0% versus 2.5%), or to pregnancies unexposed to fosfomycin and nitrofurantoin (2.0% versus 2.1%). It occurred that there was no increased risk of major CA after fosfomycin exposure during the first trimester of pregnancy [22]. Regarding adverse reactions following the single-dose administration of fosfomycin, gastrointestinal disorders (diarrhea, vomiting, nausea, abdominal pain) are the most common events that are usually self-limited in duration and resolve spontaneously. Apart from that, dysgeusia, allergic reactions (erythematous skin

eruptions, urticaria, hypersensitivity, pruritus), and ionic imbalance are reported frequently [17,23,24]. In a previously mentioned work by Schulz et al., six of nine selected studies assessed the adverse effects reported by the groups. In one case, the most commonly reported adverse effect was diarrhea, with an incidence of 10.7% in the single-dose fosfomycin group. Another analyzed study reported 12 cases of adverse effects (nausea, vomiting, and diarrhea), where only one case belonged to the fosfomycin single-dose group (11 occurred in the amoxicillin-clavulanate group) [20]. There were also few reports of dyspnea, fatigue, limb/back pain, hypokalemia, edema, and phlebitis [17,23,24]. Unlike sulfonamides or quinolones, fosfomycin is a safe alternative to β-lactams for treating urinary tract infections in pregnant women [19].

Conclusion

Urinary tract infections (UTIs) and asymptomatic bacteriuria (ASB) during pregnancy are common and troublesome problems. Fortunately, these infections are most often easily treated with good outcomes. Rarely, when ignored, UTIs may lead to several complications and become an essential cause of maternofetal morbidity and mortality. Therefore, all pregnant women with UTI require adequate treatment. Fosfomycin is a clinically effective and safe antibiotic (with continuously low resistance rates and low potential to cause collateral damage like *Clostridium difficile* infection) recommended in numerous countries for the treatment of UTIs or ASB in non-pregnant and pregnant women.

Conflict of interest
None

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References

1. Ansaldi Y, Martinez de Tejada Weber B. Urinary tract infections in pregnancy. Clin Microbiol Infect. 2022:S1198-743X(22)00431-1.
2. Balachandran L, Jacob L, Al Awadhi R, et al. Urinary Tract Infection in Pregnancy and Its Effects on Maternal and Perinatal Outcome: A Retrospective Study. Cureus. 2022;14(1):e21500.
3. Corrales M, Corrales-Acosta E, Corrales-Riveros JG. Which Antibiotic for Urinary Tract Infections in Pregnancy? A Literature Review of International Guidelines. J Clin Med. 2022;11(23):7226.
4. Johnson CY, Rocheleau CM, Howley MM, et al. Characteristics of Women with Urinary Tract Infection in Pregnancy. J Womens Health (Larchmt). 2021;30(11):1556-64.
5. Habak PJ, Griggs, Jr RP. Urinary Tract Infection In Pregnancy. 2022 Jul 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
6. Kalinderi K, Delkos D, Kalinderis M, et al. Urinary tract infection during pregnancy: current concepts on a common multifaceted problem. J Obstet Gynaecol. 2018;38(4):448-53.
7. Ciciu E, Paşatu-Cornea AM, Petcu LC, et al. Early diagnosis and management of maternal ureterohydronephrosis during pregnancy. Exp Ther Med. 2022;23(1):27.
8. DeYoung TH, Whittington JR, Ennen CS, et al. Pyelonephritis in Pregnancy: Relationship of Fever and Maternal Morbidity. AJP Rep. 2019;9(4):e366-e71.
9. Dijkmans AC, Zacarías NVO, Burggraaf J, et al. Fosfomycin: Pharmacological, Clinical and Future Perspectives. Antibiotics (Basel). 2017 31;6(4):24.
10. Marino A, Stracquadanio S, Bellanca CM, et al. Oral Fosfomycin Formulation in Bacterial Prostatitis: New Role for an Old Molecule-Brief Literature Review and Clinical Considerations. Infect Dis Rep. 2022;14(4):621-34.
11. Marino A, Stracquadanio S, Campanella E, et al. Intravenous Fosfomycin: A Potential Good Partner for Cefiderocol. Clinical Experience and Considerations. Antibiotics. 2023;12(1):49.
12. Díez-Aguilar M, Cantón R. New microbiological aspects of fosfomycin. Rev Esp Quimioter. 2019;32(1):8-18.
13. López-Montesinos I, Horcajada JP. Oral and intravenous fosfomycin in complicated urinary tract infections. Rev Esp Quimioter. 2019;32(1):37-44.
14. Saeed NK, Al Khawaja S, Al-Biltagi M. Antimicrobial Susceptibilities of Urinary Extended-spectrum β-lactamase Escherichia coli to Fosfomycin. Oman Med J. 2021;36(6):e314.
15. Falagas ME, Vouloumanou EK, Samonis G, et al. Fosfomycin. Clin Microbiol Rev. 2016;29(2):321-47.

16. www.urpl.gov.pl (access date 10.01.23).
17. www.ema.europa.eu (access date 11.01.23).
18. Konwar M, Gogtay NJ, Ravi R, et al. Evaluation of efficacy and safety of fosfomycin versus nitrofurantoin for the treatment of uncomplicated lower urinary tract infection (UTI) in women - A systematic review and meta-analysis. J Chemother. 2022;34(3):139-48.
19. Wang T, Wu G, Wang J, et al. Comparison of single-dose fosfomycin tromethamine and other antibiotics for lower uncomplicated urinary tract infection in women and asymptomatic bacteriuria in pregnant women: A systematic review and meta-analysis. Int J Antimicrob Agents. 2020;56(1):106018.
20. Schulz GS, Schütz F, Spielmann FVJ, et al. Single-dose antibiotic therapy for urinary infections during pregnancy: A systematic review and meta-analysis of randomized clinical trials. Int J Gynaecol Obstet. 2022;159(1):56-64.
21. Philipps W, Fietz AK, Meixner K, et al. Pregnancy outcome after first-trimester exposure to fosfomycin for the treatment of urinary tract infection: an observational cohort study. Infection. 2020;48(1):57-64.
22. Benevent J, Araujo M, Beau AB. et al. First trimester pregnancy exposure to fosfomycin and risk of major congenital anomaly: a comparative study in the EFEMERIS database. Infection. 2023;51(1):137-46.
23. Iarikov D, Wassel R, Farley J, et al. Adverse Events Associated with Fosfomycin Use: Review of the Literature and Analyses of the FDA Adverse Event Reporting System Database. Infect Dis Ther. 2015;4(4):433-58.
24. Sojo-Dorado J, López-Hernández I, Rosso-Fernandez C, et al. Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant Escherichia coli Bacteremic Urinary Tract Infections: A Randomized Clinical Trial. JAMA Netw Open. 2022;5(1):e2137277.