

Research Article

Comparison of the Therapeutic Effect of Cranberry against Nitrofurantoin in Preventing Recurrent Cystitis during Pregnancy

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A B S T R A C T

Background: Cystitis is an inflammation of the urinary bladder due to bacterial or non-bacterial causes. Signs and symptoms of cystitis are difficult to distinguish in pregnancy. Nitrofurantoin can stop the symptoms of cystitis and may lower the chance of some pregnancy problems including preterm delivery. Though cranberry is used to prevent or treat urinary tract infections, scientific evidence to support the use of cranberry for the prevention or treatment of cystitis is lacking.

Objective: To evaluate the therapeutic effectiveness of cranberry in preventing recurrent cystitis during pregnancy and compare it with that of nitrofurantoin

Methods: One hundred pregnant women were divided as follows: Group 1 included 50 women with cystitis kept on nitrofurantoin (100 mg per day) given orally till the gestation age reached 32 weeks, and Group 2 included 50 women with cystitis kept on cranberry capsule (one capsule per day) given orally till the end of gestation. Patients were clinically examined and urine samples were analyzed monthly to evaluate the presence of bacteria and pus cells.

Results: Nitrofurantoin and cranberry showed an increase in the number of asymptomatic patients on comprehensive clinical examination; also, urinalysis showed that the number of patients with the absence of bacteria and pus cells in urine increased and there was a decrease in the number of positive (++) category cases, which indicated that the pregnant women showed improvement.

Conclusion: Both nitrofurantoin and cranberry were therapeutically effective in the treatment of cystitis, but the therapeutic effectiveness of nitrofurantoin is higher as compared to that of cranberry.

Keywords: Cystitis, Nitrofurantoin, Cranberry, Pregnant Women

Introduction

Infection of the urinary tract is prevalent all over the world, affecting all ages and genders. The most common type of UTI is cystitis, which is an inflammation in the urinary bladder. According to the complexity of cystitis, it can be classified into complicated and uncomplicated types. Uncomplicated cystitis refers to lower urinary tract infection (UTI) in either men or non-pregnant women who are otherwise healthy.⁽¹⁾ There are different causes of acute cystitis; the most common cause being bacterial infection in the bladder.

Complicated cystitis is a more serious form in which there are many risk factors that make it highly dangerous and less responsive to antibacterial therapy. Acute cystitis is typically caused by a bacterial infection of the urinary bladder.²

Acute cystitis affects both genders, however, females are more likely to be susceptible to this infection due to particular anatomical characteristics like close proximity of the rectum to the urethral meatus as well as a relatively shorter urethral length.

Escherichia coli bacteria is the most common cause of cystitis with 75% to 95% of cases caused by it. Klebsiella is the second most common cause of cystitis.³

Clinical examination and the appearance of symptoms such as dysuria, urgency, and frequency in afebrile patients are considered important tools in the diagnosis of cystitis. The presence of bacteria and pus cells in urine is another important diagnostic tool. Up to 30% of patients with untreated asymptomatic bacteriuria later develop symptomatic cystitis.⁴ Not all patients with cystitis are associated with symptoms. In a study, it was found that 1.3% of obstetric patients who delivered babies developed acute cystitis with no symptoms of pyelonephritis.⁵

Acute cystitis is treated with antibiotic therapy. The choice of the antibacterial drug depends on different criteria. The most important one is the culture of the sample to detect the sensitivity of the bacteria to a particular type of antibacterial agent. Antibiotics commonly used include amoxicillin, ampicillin, cephalosporin, nitrofurantoin, and trimethoprim-sulfamethoxazole.⁶

One of the most important herbal remedies used to treat cystitis is cranberry. Cranberry, which belongs to *Vaccinium macrocarpon* Aiton, also known as American cranberry, is a fruit cultivated in North America. It has been used traditionally against urinary tract infections (UTIs).⁷

Cranberry is considered a good choice for the treatment of UTIs in pregnant women. Cranberries contain proanthocyanidins (PACs), substances that can prevent bacteria from sticking to the walls of the bladder. This may help prevent infections and reduce the need for people

to spare time for medical appointments. However, there is currently no established regimen for what PACs to use and no formal regulation by health authorities regarding cranberry products. In particular, the dose suggested may not be included in the package.⁸

Therefore, a case-control study was planned involving asymptomatic bacteriuria and recurrent cystitis among pregnant women in order to prevent complications such as premature rupture of membranes (PROM), preterm labour (PTL), and complications in their foetuses.

Methodology

A case-control study was conducted involving 100 pregnant women from the private clinics who enrolled for the study from June 2022 to June 2023 in Iraq. Ethical approval was obtained from college of medicine/ ibn-sina university of medicine and pharmaceutical sciences for Ethics Committee These pregnant women were divided into the following two groups:

- **Group 1:** 50 pregnant women with cystitis kept on nitrofurantoin (100 mg per day) given orally till the gestation age reached 32 weeks.
- **Group 2:** 50 pregnant women with cystitis kept on cranberry capsules (one capsule per day) given orally till the end of gestation.

Pregnant women in the age range of 21–35 years, having a gestational age ranging from 24 to 32 weeks, and free from chronic diseases like diabetes mellitus, hypertension or any chronic kidney diseases like pyelonephritis; pregnant women with no risk of preterm labour and genital tract abnormalities; and pregnant women having normal amniotic fluid index as examined by ultrasound were included in the study.

Pregnant women less than 20 years or more than 35 years of age; pregnant women with a gestational age of less than 24 weeks or more than 32 weeks; pregnant women with any chronic disease; and pregnant women at risk of preterm labour; first trimester of pregnancy, the crown-rump length (CRL) were excluded from the study.

Measurement Parameters

Ultrasound Evaluation for Pregnancy

Gestational age at enrolment was determined using diagnostic ultrasound (US) imaging equipment (FFSonic UF-4100) with a 3.5 MHz transducer for transabdominal examination generally and a 5 MHz transducer for very thin women. Gestational age was calculated based on biparietal diameter, abdominal circumference, and femur length⁹ using standard algorithms¹⁰. For women in the first trimester of pregnancy, the crown-rump length (CRL) was used to confirm exclusion from the study as mentioned above.

Microscopic Sediment Urinalysis

Manual microscopic sediment inspection was performed as follows: each urine sample (10 mL) was centrifuged at 1,500 rpm for 5 min, and the supernatant was removed. At least 20 random microscopic fields were examined at 40x high power field (HPF) for each sample, and the mean number of cells and particles/ HPF were calculated.¹¹

Statistical Analysis

The categorical data were expressed as frequency and percentage. The decrease percentage was measured as follows: [(new read-old read)/old read]*100.

Results

As shown in Table 1, in the case of pregnant women taking nitrofurantoin at a dose of 100 mg/kg, a decrease in the number of symptomatic cases was seen on comparing the results of the first and second examinations and the percentage decrease was 39.0%. At the same time, there was an increase in the asymptomatic patients in the second examination as compared to the first one, the percentage decrease being -50.0%. In the case of patients who took cranberry capsules, a decrease in the symptomatic cases (9.5%) and an increase in the asymptomatic cases (-16.6%) was observed in the second examination when compared to the first one.

A decrease in symptomatic cases (52.9%) was seen on comparing the results of the second and third examinations in the case of pregnant women taking nitrofurantoin, while an increase was seen in the number of asymptomatic cases (-24.2%). Meanwhile, in the case of patients who took cranberry capsules, a decrease in the symptomatic

cases (37.9%) and an increase in the asymptomatic cases (-52.4%) was observed on comparing the results of the second and first examinations.

As shown in Table 2, an increase in bacteria was observed in urine on comparing the results of the first and second examinations in the case of pregnant women taking nitrofurantoin at a dose of 100 mg/kg for the categories (no and +), the changes in percentages being 50.0% and 69.0%, respectively. At the same time, there was a decrease in the bacterial count in urine in category (++) patients on comparing the results of these two examinations (-86.0%). Meanwhile, for the patients who took cranberry capsules, a comparison of the results of the second and first examinations showed that there was an increase in bacteria in urine for the categories (no and +), the percentage change being 200.0% and 63.0%, respectively, and a decrease in the bacteriuria in category (++) the percentage change being -59.0%.

An increase in bacteria was seen in the urine of pregnant women taking nitrofurantoin at a dose of 100 mg/kg on comparison of the results of the second and third examinations for the category (no) in which the percentage of change was 200.0%. At the same time, a decrease in the bacterial count in urine in category (+ and ++) patients was found on comparing these two examinations (-9.0% and -67.0%, respectively). Meanwhile, on comparing the results of the second and third examinations in the case of patients who took cranberry capsules, it was found that there was an increase in bacteria in urine for the categories (no and +) (33.0% and 11.0%, respectively) and a decrease in bacteriuria in category (++) (-45.0%).

Table 1. Effect of Nitrofurantoin and Cranberry Capsules on the Appearance/ Disappearance of Symptoms in Pregnant Women with Cystitis

Appearance/ Disappearance of Symptoms	First Examination		Second Examination		Third Examination	
	Symptomatic n	Asymptomatic n	Symptomatic n (%)	Asymptomatic n (%)	Symptomatic n (%)	Asymptomatic n (%)
Nitrofurantoin (100 mg/day)	28	22	17 (39.0)	33 (-50.0)	8 (52.9)	41 (-24.2)
Cranberry capsule	32	18	29 (9.5)	21 (-16.6)	18 (37.9)	32 (-52.4)

Each group contained 50 pregnant women with cystitis.

Data were expressed as frequency, and the value between two brackets represents the percentage decrease.

Table 2. Effect of Nitrofurantoin and Cranberry Capsules on the Presence of Bacteria in Urine of Pregnant Women with Cystitis

Bacteria	First Examination			Second Examination			Third Examination		
	no n	+	++	no n (%)	+	++	no n (%)	+	++
Nitrofurantoin (100 mg/day)	2	26	22	3 (50.0)	44 (69.0)	3 (-86.0)	9 (200.0)	40 (-9.0)	1 (-67.0)
Cranberry capsule	1	22	27	3 (200.0)	36 (63.0)	11 (-59.0)	4 (33.0)	40 (11.0)	6 (-45.0)

Each group contained 50 pregnant women with cystitis.

Data were expressed as frequency, and the value between two brackets represents the percentage decrease.

No mean there are less than 10 wbc/HPF, + there is 10-15 WBC/HPF, ++ mean there are 20-25WBC/HPF

Table 3. Effect of Nitrofurantoin and Cranberry Capsules on the Presence of Pus in Urine of Pregnant Women with Cystitis

Pus	First Examination			Second Examination			Third Examination		
	no n	+	++	no n (%)	+	++	no n (%)	+	++
Nitrofurantoin (100 mg/day)	3	30	17	14 (366.0)	22 (-27.0)	14 (-17.0)	20 (42.0)	21 (-4.5)	9 (-35.0)
Cranberry capsule	2	33	15	7 (250.0)	34 (3.0)	9 (-40.0)	11 (57)	31 (-8.8)	8 (-11.0)

Each group contained 50 pregnant women with cystitis.

Data were expressed as frequency, and the value between two brackets represents the percentage decrease.

No mean there are less than 10 wbc/HPF, + there is 10-15 WBC/HPF, ++ mean there are 20-25WBC/HPF

As seen in Table 3, an increase in pus cells was observed in the urine of pregnant women taking nitrofurantoin at a dose of 100 mg/kg on comparing the results of the first and second examinations for the category (no) in which the percentage change was 366.0%. At the same time, there was a decrease in the pus cells in urine in category (+ and ++) patients when compared between these two examinations (-27.0% and -17.0%, respectively). Meanwhile, for the patients who took cranberry capsules, a comparison of the second examination with the first examination showed that there was an increase in pus cells in urine for the following category (no and +) patients (250.0% and 3.0%, respectively) and a decrease in the pus cells in category (++) (-40.0%).

An increase in pus cells was seen in the urine of pregnant women taking nitrofurantoin at a dose of 100 mg/kg in the (no) category on comparing the results of the second and third examinations, in which the percentage decrease was 42.0%. At the same time, there was a decrease in the pus count in urine in category (+ and ++) patients on comparison between these two examinations (-4.5% and -35.0%, respectively). Meanwhile, for the patients who took

cranberry capsules, a comparison of the third examination with the second examination revealed that there was an increase in pus in urine in the (no) category (57.0%) and a decrease in pus in category (+ and ++) patients (-8.8% and -11.0%, respectively).

Discussion

Cystitis is a type of urinary tract infection associated with a burning sensation. Normally, urine is sterile, but during pregnancy, physiological changes in the pregnant urinary tract lead to infection. The dilatation in the urethra sometimes is seen due to compression of the ureters by the gravid uterus.¹² Many factors increase the risk of cystitis, one of them being hormonal changes. Hormones, like progesterone, cause smooth muscle relaxation leading to dilation and urinary stasis, and an increase in vesicoureteral reflux.¹³

Bacterial infection in the urinary system, particularly *E. coli*, is considered the major cause of cystitis.¹⁴ Pregnancy is a state of relative immune-compromise. This immune-compromised state may be another cause for the increased frequency of UTIs seen in pregnancy.¹⁵

The uncomplicated type of cystitis is considered to be easier to treat, it needs only three days of antibacterial therapy to get cured; meanwhile, the complicated type or recurrent cystitis, which affects about 25% of women, needs a longer duration of treatment.¹⁶ Antibacterial agents are the first choice for treatment but sometimes physicians may use catheter drainage to treat urine retention, incomplete bladder emptying and/ or haematuria. A surgical operation is sometimes indicated if there is partial or complete resection.¹⁷

Nitrofurantoin is an antibiotic of choice for simple cystitis with a high cure rate ranging from 79% to 92%.¹⁸ It is safely used in pregnancy to treat cystitis.¹⁹ Previous animal studies have demonstrated that there is no obvious problem with foetal exposure to this antibiotic.²⁰

A previous study was used to evaluate the therapeutic effect of nitrofurantoin in the treatment of cystitis. This randomised controlled study was conducted on 338 symptomatic women with cystitis in good general health. They found that these patients were completely cured after 30 days of treatment.²¹ This finding is in agreement with the results of the present study which showed a decrease in the pus cells and bacteria in urine along with the disappearance of symptoms, leading to the improvement in the health of pregnant women.

Cranberry is a folk remedy for the treatment of different types of urinary tract infections; one of these infections being cystitis. Previous studies have focused on its mechanism of action besides its pharmacokinetics.²² One of these previous studies was conducted to examine the therapeutic effectiveness of cranberry in cystitis prevention on a total of 1,049 patients. They concluded that there is some evidence that cranberry juice may decrease the incidence of symptomatic cystitis over a 12-month period, particularly, and only for women with recurrent UTIs.²³ Their findings are similar to the results of the present study, in which the use of cranberry in pregnant women causes a decrease in the symptoms of cystitis and an increase in the non-bacterial and pus status in their urine, which indicates its therapeutic benefit.

Conclusion

The use of cranberry capsules for pregnant women with cystitis has a therapeutic benefit in preventing recurrent cystitis during pregnancy, but its therapeutic benefit is less effective as compared to that of nitrofurantoin.

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Conflict of Interest

The authors declare that the research was conducted in

the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019 Sep;33(9):e13507. [PubMed] [Google Scholar]
2. Duane S, Vellinga A, Murphy AW, Cormican M, Smyth A, Healy P, Moore M, Little P, Devane D. COSUTI: a protocol for the development of a core outcome set (COS) for interventions for the treatment of uncomplicated urinary tract infection (UTI) in adults. *Trials*. 2019;20(1):106. [PubMed] [Google Scholar]
3. Behzadi P, Behzadi E, Yazdanbod H, Aghapour R, Cheshmeh MA, Omran DS. A survey on urinary tract infections associated with the three most common uropathogenic bacteria. *Maedica (Bucur)*. 2010 Apr;5(2):111-5. [PubMed]
4. Heitmann K, Nordeng H, Holst L. Pregnancy outcome after use of cranberry in pregnancy--the Norwegian Mother and Child Cohort Study. *BMC Complement Altern Med*. 2013 Dec 7;13:345. [PubMed] [Google Scholar]
5. Nordeng H, Bayne K, Havnen GC, Paulsen BS. Use of herbal drugs during pregnancy among 600 Norwegian women in relation to concurrent use of conventional drugs and pregnancy outcome. *Complement Ther Clin Pract*. 2011;17(3):147-51. [PubMed] [Google Scholar]
6. Hanlon JT, Perera S, Drinka PJ, Crnich CJ, Schweon SJ, Klein-Fedyshin M, Wessel CB, Saracco S, Anderson G, Mulligan M, Nace DA. The IOU Consensus Recommendations for empirical therapy of cystitis in nursing home residents. *J Am Geriatr Soc*. 2019 Mar;67(3):539-45. [PubMed] [Google Scholar]
7. Micali S, Isgro G, Bianchi G, Miceli N, Calapai G, Navarra M. Cranberry and recurrent cystitis: more than marketing? *Crit Rev Food Sci Nutr*. 2014;54(8):1063-75. [PubMed] [Google Scholar]
8. Luczak T, Swanoski M. A review of cranberry use for preventing urinary tract infections in older adults. *Consult Pharm*. 2018 Aug 1;33(8):450-3. [PubMed] [Google Scholar]
9. MiP: Ultrasound reference manual for pregnancy dating: Developed for the Assessing the Safety of Antimalarials during early Pregnancy (ASAP) Study through support from the Malaria in Pregnancy Consortium (MiPc). University of Washington: Department of Global Health; 2012.
10. Fung R, Villar J, Dashti A, Ismail LC, Staines-Urias E, Ohuma EO, Salomon LJ, Victora CG, Barros FC, Lambert A, Carvalho M, Jaffer YA, Noble JA, Gravett MG, Purwar M, Pang R, Bertino E, Munim S, Min AM, McGready R,

- Norris SA, Bhutta ZA, Kennedy SH, Papageorghiou AT, Ourmazd A; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). Achieving accurate estimates of fetal gestational age and personalised predictions of fetal growth based on data from an international prospective cohort study: a population-based machine learning study. *Lancet Digit Health*. 2020 Jun 23;2(7):e368-75. [PubMed] [Google Scholar]
11. Karah N, Rafei R, Elamin W, Ghazy A, Abbara A, Hamze M, Uhlin BE. Guideline for urine culture and biochemical identification of bacterial urinary pathogens in low-resource settings. *Diagnostics (Basel)*. 2020 Oct 16;10(10):832. [PubMed] [Google Scholar]
 12. Rank EL, Lodise T, Avery L, Bankert E, Dobson E, Dumyati G, Hassett S, Keller M, Pearsall M, Lubowski T, Carreno JJ. Antimicrobial susceptibility trends observed in urinary pathogens obtained from New York state. *Open Forum Infect Dis*. 2018 Nov;5(11):ofy297. [PubMed] [Google Scholar]
 13. Committee Opinion No. 717: sulfonamides, nitrofurantoin, and risk of birth defects. *Obstet Gynecol*. 2017 Sep;130(3):e150-2. [PubMed]
 14. Cutts JC, Agius PA, Lin Z, Powell R, Moore K, Draper B, Simpson JA, Fowkes FJ. Pregnancy-specific malarial immunity and risk of malaria in pregnancy and adverse birth outcomes: a systematic review. *BMC Med*. 2020;18(1):14. [PubMed] [Google Scholar]
 15. Shi H, Kang CI, Cho SY, Huh K, Chung DR, Peck KR. Follow-up blood cultures add little value in the management of bacteremic urinary tract infections. *Eur J Clin Microbiol Infect Dis*. 2019 Apr;38(4):695-702. [PubMed] [Google Scholar]
 16. Gomila A, Carratalà J, Eliakim-Raz N, Shaw E, Wiegand I, Vallejo-Torres L, Gorostiza A, Vigo JM, Morris S, Stoddart M, Grier S, Vank C, Cuperus N, dan Heuvel LV, Vuong C, MacGowan A, Leibovici L, Addy I, Pujol M; COMBACTE MAGNET WP5 RESCUING Study Group and Study Sites. Risk factors and prognosis of complicated urinary tract infections caused by *Pseudomonas aeruginosa* in hospitalized patients: a retrospective multicenter cohort study. *Infect Drug Resist*. 2018;11:2571-81. [PubMed] [Google Scholar]
 17. McKinnell JA, Stollenwerk NS, Jung CW, Miller LG. Nitrofurantoin compares favorably to recommended agents as empirical treatment of uncomplicated urinary tract infections in a decision and cost analysis. *Mayo Clin Proc*. 2011 Jun;86(6):480-8. [PubMed] [Google Scholar]
 18. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother*. 2015 Sep;70(9):2456-64. [PubMed] [Google Scholar]
 19. Le J, Briggs GG, McKeown A, Bustillo G. Urinary tract infections during pregnancy. *Ann Pharmacother*. 2004;38(10):1692-701. [PubMed] [Google Scholar]
 20. Prytherch JP, Sutton ML, Denine EP. General reproduction, perinatal-postnatal, and teratology studies of nitrofurantoin macrocrystals in rats and rabbits. *J Toxicol Environ Health*. 1984;13(4-6):811-23. [PubMed] [Google Scholar]
 21. Fekete T. 5 days of nitrofurantoin was equivalent to 3 days of trimethoprim-sulfamethoxazole for women with non-complicated cystitis. *Evid Based Med*. 2008;13(3):80. [PubMed] [Google Scholar]
 22. Hisano M, Bruschini H, Nicodemo AC, Srougi M. Cranberries and lower urinary tract infection prevention. *Clinics (Sao Paulo)*. 2012;67(6):661-8. [PubMed] [Google Scholar]
 23. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2008;(1):CD001321. [PubMed] [Google Scholar]