



Original Article

Comparison of Clinical Response to D-Mannose with Behavioral Modifications Versus Behavioral Modifications Alone in Asymptomatic Pyuria During Pregnancy

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ABSTRACT

The physiological and structural changes during pregnancy cause ureteral dilatation and urine stasis, which can lead to asymptomatic and symptomatic infections. **Objective:** To compare the clinical response between d-mannose with behavioral modifications versus behavioral modifications alone in asymptomatic pyuria during pregnancy. **Methods:** A quasi experimental study was conducted from April to September 2021, in the Department of Gynecology and Obstetrics Maternal and Child Health Center unit-1, PIMS, Islamabad. A total of 130 women with diagnoses of asymptomatic pyuria matching the inclusion criteria were recruited during study period and assigned to two groups by consecutive non-probability sampling method. Patients with urinary tract abnormalities, GDM, and antibiotic-treated symptomatic UTIs were excluded. Group A was instructed to take 1 g of D-mannose twice daily and follow the advises about behavioral changes. The group B was instructed to follow behavioral change only. pus cells in urine R.E. reports were used to evaluate response of treatments. **Results:** According to the study, the mean age of patients in group A was 27.69 ± 4.04 years, whereas group B had a mean age of 28.85 ± 4.12 years. The majority of patients (61.54%) were aged 15-30. Patients in group A had a mean gestational age of 23.72 ± 3.19 weeks, whereas group B had 24.26 ± 3.23 weeks. Patients had a mean BMI of 29.65 ± 3.55 kg/m². In group A; 23 (35.18%) and in group B 11 (16.92%) cases of asymptomatic pyuria achieved resolution. **Conclusions:** This study found that D-mannose with behavioral adjustments resolves asymptomatic pyuria during pregnancy better than behavioral modifications alone.

INTRODUCTION

During pregnancy, the physiological and anatomical changes are responsible for ureteral dilatation urinary stasis that facilitates the development of asymptomatic and symptomatic infections in women [1, 2]. The reported incidence of asymptomatic infection ranges from 2% to 12% in pregnant women. About 30-40% of the untreated pregnant women who have the asymptomatic urinary tract infection (bacteriuria /pyuria) will ultimately develop acute pyelonephritis, intrauterine growth retardation, and low birth weight, preterm labour [3-5]. Unfavorable maternal and perinatal outcomes are linked to untreated bacteriuria during pregnancy. Preterm birth, hypertensive problems,

intrauterine growth restriction (IUGR), recurrent abortions, oligohydramnios and polyhydramnios, early rupture of the membranes, and labour induction are all independently linked to asymptomatic bacteriuria (ASB) [6]. Furthermore, throughout puberty, ASB raises the chance of pyelonephritis. Therefore, it has been recommended that all pregnant women attending an antenatal clinic, even in the absence of the symptoms, be regularly screened to avoid unfavorable problems in the baby and mother that may emerge owing to ASB [7]. Whether the infection is symptomatic or asymptomatic, pregnant women with UTIs are now treated with a brief course of antibiotics. An

increase in antimicrobial resistance (AMR) is closely linked to the unnecessary or excessive use of antibiotics. Therefore, alternative therapies have been studied, such as cranberry juice and D-mannose. D-mannose is a sugar found in some fruits [8]. In human metabolism, D-mannose plays a role in the glycosylation of certain proteins. D-mannose is similar to the glycoprotein receptors on urothelial cells. Experiments have demonstrated that D-mannose binds to FimH adhesions present in fimbria of enteric bacteria and acts as a competitive inhibitor for bacterial adherence to urothelial receptors [9]. Therefore, if a sufficient amount of D-mannose is present in urine, then FimH adhesion will be saturated, so urothelial receptors are spared from bacterial adhesion. Ala-Jaakkola R *et al.*, compared the efficacy of D-mannose with trimethoprim/sulphamethoxazole TMP/SMX in the prevention of urinary tract infection with results of mean time to recurrence 200 days in the D-mannose group, 52.7 days for the antibiotic group [10, 11]. Hayward *et al.*, compared D-mannose with nitrofurantoin [12]. Results favored the D-mannose group as an effective therapy for urinary tract infections. The recurrence rate of acute urinary tract infection in the D-mannose study group was 14.6%, while in the antibiotic group, it was 20.4%. Another study demonstrated the efficacy of D-mannose alone in managing acute urinary tract infections. This study displayed that the acute infection rate in the D-mannose group was 4.5%, while it was 33.3% in the placebo/no treatment group [12].

Studies have demonstrated the ability of D-mannose-like molecules to reduce bacterial load. So far, no study in Pakistan has been conducted to evaluate the efficacy of D-mannose in asymptomatic pyuria. Thus, the current study aimed to assess the role of D-mannose in resolving asymptomatic pyuria and recommend better treatment with less morbidity.

METHODS

A quasi experimental study was conducted from April to September 2021 in the Department of Gynecology and Obstetrics Maternal and Child Health Center unit-1, PIMS, Islamabad after the approval of the ethical review board (Ref No.F.1-1/2015/ERB/SZABMU/545). Patients with absence of any symptoms of urinary tract infections (UTI) with 15 or more white blood cells/ μL on urine analysis report were included. Patients were excluded those with a history of urinary tract anomalies, pyelonephritis, history of antibiotics intake for symptomatic UTI, gestational diabetes, and systemic inflammatory urinary tract infections. Patients who fulfill the inclusion criteria were offered to participate in the study after informed verbal and written consent. A total of 130 women diagnosed with asymptomatic pyuria matching the inclusion criteria were recruited during study period and assigned to two groups

by consecutive non-probability sampling method. The sample size was calculated using WHO sample size calculator with 5% level of significance and 80% power of test. With 65 subjects in each group, the total size was 130. Group A was instructed to take 1g twice daily of D-mannose (dietary supplement) for 5 days. Group B encountered no treatment and was the placebo group. Both groups were taught about behavioral modifications, i.e., drinking plenty of fluids (10-12 glasses a day), observing proper hygienic measures (washing front to back after the use of the toilet), frequency of urination, pre and post-coital voiding, complete bladder emptying before sleep). All patients were contacted by mobile phone to follow the advice and notified if any symptoms appeared. Urine Routine Examination (URE) was performed through laboratory after 5 days of therapy. Results of the study were assessed on the ability of either treatment plan to reduce white blood cells /pus cells on urine RE report i.e. <15 pus cells per μL . Resolution of pus cells ≥ 15 per μL of urine were regarded under asymptomatic pyuria. The collected data were analyzed by using the SPSS 23.0 version. Mean \pm SD was calculated for age, BMI and gestational age. The outcome variable was calculated using frequency and percentages. A chi-square statistical significance test was applied to measure the frequency of pyuria between the two groups. p-value <0.05 was considered statistically significant.

RESULTS

This current enrolled 130 patients, with 65 patients in each group. The mean age of patients in group A was 27.69 ± 4.04 years, and in group B was 28.85 ± 4.12 years. The overall mean age of patients was 28.32 ± 4.09 years. Most of the patients in the current study were from the 15-30 age group, i.e., 61.54%. The mean gestational age of patients in group A was 23.72 ± 3.19 weeks, and in group B was 24.26 ± 3.23 weeks. The overall mean gestational age of patients was 23.89 ± 3.20 weeks. Most patients in the current study were from the >24 weeks gestational age group, i.e., 56.15%. The mean BMI of patients in group A was 30.03 ± 3.54 kg/m² and 29.52 ± 3.58 kg/m² in group B. The overall mean BMI of patients was 29.65 ± 3.55 kg/m². Most patients in the current study were from the >30 BMI group, i.e., 53.85% (Table 1).

Table 1: Results of Age, Gestational and BMI in Study Groups (n=65)

Variables	Category	Study Groups		Total N (%) / (Mean \pm SD)
		Group A N (%) / (Mean \pm SD)	Group B N (%) / (Mean \pm SD)	
Age (Years)	15-30	44 (67.69%)	36 (55.0%)	80 (61.54%)
	31-45	21 (32.31%)	29 (45.0%)	50 (38.46%)
	Mean	27.69 ± 4.04	28.85 ± 4.12	28.32 ± 4.09
Gestational Age (Weeks)	13-24	30 (46.15%)	27 (41.54%)	57 (43.85%)
	>24	35 (53.85%)	38 (58.46%)	73 (56.15%)
	Mean	23.72 ± 3.19	24.26 ± 3.23	23.89 ± 3.20

BMI (Kg/m ²)	≤30	27 (41.54%)	33 (50.77%)	60 (46.15%)
	>30	38 (58.46%)	32 (49.23%)	70 (53.85%)
	Mean	30.03 ± 3.54	29.52 ± 3.58	29.65 ± 3.55

This study found that the frequency for resolution of asymptomatic pyuria in group A was 23 (35.38%), and in group B, it was 11 (16.92%) with a significant p-value (p=0.017). These were detected by the presence of pus cells/WBCs ≥ 15 per µL of urine. Group A showed better results than Group B (Table 2).

Table 2: Results of Resolution of Asymptomatic Pyuria (n=65)

Resolution of Asymptomatic Pyuria	Study Groups		Total N (%)	p-value
	Group A N (%)	Group B N (%)		
Yes	23 (35.38%)	11 (16.92%)	34 (25.19%)	0.017*
No	42 (64.62%)	54 (83.08%)	96 (71.11%)	
Total	65 (100.0%)	65 (100.0%)	130 (100.0%)	

*Significance Level (p<0.05)

The stratification results of the resolution of asymptomatic pyuria with different variables were given in table 3.

Table 3: Stratification Results of Resolution of Asymptomatic Pyuria with Different Variables (n=65)

Variables	Category	Resolution of Asymptomatic Pyuria			
		Group A N (%)		Group B N (%)	
		Yes	No	Yes	No
Age of Patients (Years)	15-30	18 (40.91%)	26 (59.09%)	06 (16.67%)	30 (83.33%)
	31-45	05 (23.81%)	16 (76.19%)	05 (17.24%)	24 (82.76%)
GA (Weeks)	13-24	07 (23.33%)	23 (76.67%)	03 (11.11%)	24 (88.89%)
	>24	16 (45.71%)	19 (54.29%)	08 (21.05%)	30 (78.95%)
BMI (Kg/m ²)	≤30	08 (29.63%)	19 (70.37%)	05 (15.15%)	28 (84.85%)
	>30	15 (39.47%)	23 (60.53%)	06 (18.75%)	26 (81.25%)

DISCUSSION

One effective non-antibiotic preventive method is D-mannose. It is an inactive monosaccharide that prevents germs from adhering to the urothelium. It is broken down and eliminated in urine. D-mannose is a simple sugar crucial to human metabolism because it causes proteins to become glycosylated [13]. Specifically, D-mannose functions as a competitive inhibitor of bacterial adhesion to receptors of urothelial cells by binding to and blocking FimH adhesins on the tip of type 1 bacterial fimbriae. Type 1 pili have been seen on *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Shigella flexneri*, *Serratia marcescens* and *Salmonella typhimurium*, among other members of the Enterobacteriaceae family. As a result, D-mannose may stop many uropathogens connected to UTIs from adhering to the urothelium [14]. This study was conducted to compare D-mannose in combination with behavioral modifications to behavioral modifications alone for resolving the frequency of asymptomatic pyuria during pregnancy. The resolution of asymptomatic pyuria was found in 35.38% of women taking D-mannose in

combination with behavioral modifications and 16.92% in women taking behavioral modifications only, p = 0.017. Results favored the D-mannose group as an effective therapy for urinary tract infections. The recurrence rate of acute urinary tract infection in the D-mannose study group was 14.6%, while in the antibiotic group, it was 20.4%. Another study demonstrated the efficacy of D-mannose alone in managing acute urinary tract infections. This study displayed that the acute infection rate in the D-mannose group was 4.5%, while it was 33.3% in the placebo/no treatment group [15]. Concentrated D-mannose pills or sachets were tested in human pilot trials at dosages ranging from 200 mg to 3 g, with potential benefits in lowering UTI symptoms or recurrence [16]. These findings support the findings of the current study. A prospective study, which included women with a history of UTIs, was conducted by Ala-Jaakkola R et al [10, 17]. An oral liquid nutritional supplement, including D-mannose, was given to women, and the safety, tolerability, and maximum tolerated dosage were checked. Efficacy regarding UTI and symptoms related to quality of life (QOL) were significantly reduced in women who use liquid nutritional supplements, including D-mannose. De Nunzio C et al., evaluated the effectiveness of D-mannose alone in treating acute UTIs in 43 women and explored the drug's potential for managing recurrences [18]. The majority of symptoms in this prospective trial significantly improved 15 days after D-mannose was administered, according to the investigators. It's interesting to note that patients were randomized into two groups sequentially one month following diagnosis. In specifics, 21 women did not get treatment, while 22 women got prophylaxis with D-mannose. In the prophylactic group, the mean time to UTI start was 43 days (± 4.1 SD), but in the other group, it was 28 days (± 5.4 SD) (p = 0.0001). Marchiori D et al., assessed the efficacy of D-mannose with antibiotic treatment to lessen the persistence of UTI in sixty women who had survived breast cancer [19]. The authors conducted a retrospective analysis of two groups of patients: 20 patients treated with antibiotics alone and 40 women treated with antibiotic treatment combined with D-mannose for six months. Compared to women treated only with antibiotics, patients treated with D-mannose showed a significant reduction in bacteria-positive urine cultures. A randomized three-arm parallel-group research with 72 women who had a history of recurrent cystitis and an acute UTI was reported by Genovese C et al. Oral D-mannose was administered to all three groups; in group A, it was linked to birch, arbutin, and berberine; in group B, it was linked to birch, arbutin, birch, and forskolin; and in group C, it was related to proanthocyanidins. There were twelve weeks in the trial. In contrast to patients recruited in group C, the authors noted that patients in groups A and B had a decreased incidence of bouts of recurrent cystitis throughout therapy and follow-up [20].

CONCLUSIONS

This study concluded that D-mannose with behavioral modifications is better than behavioral modifications alone in resolving asymptomatic pyuria during pregnancy. So, this study recommends that D-mannose with behavioral changes be advised routinely to reduce the progression of asymptomatic pyuria during pregnancy as well as the complications of pyuria.

Authors Contribution

Conceptualization: IB

Methodology: IB, SS

Formal analysis: IB

Writing, review and editing: BB, IB, SD, SZ, ZA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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