Postmenopausal Women and Urinary Tract Infection: A Literature Narrative Review

Ala'a Ibrahim Ali Matalka

Abstract

Urinary tract infection (UTI) is a serious matter of concern worldwide. Urinary tract infections affect women more than men and are caused by normal bacterial flora that enters the urinary tract via urethra from bowel, vagina, or perineum. Postmenopausal women are more prone to developing symptomatic UTI due to estrogen deficiency as a leading factor. In a study conducted by Dason, Dason & Kapoor, the incidence of single and recurrent UTIs was 27% and 3% respectively. Recurrent infection was mostly a result of bacterial re-infection or persistence. Gram negative bacteria such as- E.coli and Klebsiella spp. have been reported to be the most common UTI causing organisms. E. coli causes around 70-95% of upper and lower UTI and is the cause for 80-85% of community-acquired UTI, while Staphylococcus saprophyticus accounts for 5–10% of urinary tract infections. In very rare cases, UTI is caused by viral or fungal infections. The clinical presentation of UTI is different in postmenopausal elderly women compared with younger women. Symptoms like frequency, dysuria, hematuria, and fever are not reported by postmenopausal women, but they are likely to report flank pain. Postmenopausal women are also affected by recurrent UTI, which is defined as ≥3 UTI per year or ≥2 urinary tract infection per half year. Increased mortality rates go hand in hand with bacteriuria in elderly women; though bacteriuria is mostly asymptomatic and does not cause death; this is a major concern. The aim of this paper is to conduct a narrative review of UTI in postmenopausal women to reach a better understanding of this problem.

Keywords: Urinary tract infection, Bacteriuria, Estrogen, Postmenopausal women, Antimicrobial prophylaxis, Probiotic lactobacilli.

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Introduction

UTI includes lower urinary tract infection (acute cystitis) and upper urinary tract infection (acute pyelonephritis). These infections may be: asymptomatic (asymptomatic bacteriuria), symptomatic uncomplicated (simple) which occurs in a functionally and structurally normal urinary tract, or complicated which occur in an anatomically distorted system[1-3].

In the primary as well as secondary care setting, UTI is ranked as the second most common medical illness requiring attention and treatment, showing a dramatic increase in UTI incidence in elderly women

Risk factors of complex urinary tract

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infection are variable and multiple. Patient factors include: male child <12 years, pregnancy, intercourse, immune-suppression, personal hygiene practices, and frequency of urination. Structural or functional factors include: presence of indwelling catheter, chronic retention, bladder outflow obstruction, urologic structural abnormalities, polycystic kidneys, renal calculi, and utilization of spermicidal agents and diaphragm as contraceptive methods. Bacterial factors include multi-resistant organisms, reduced lactobacilli concentration, and nosocomial acquired infections[4].

Recently, the term genitourinary syndrome of menopause (GSM) is used to describe various menopausal signs and symptoms associated with physical changes of the vagina, vulva, and lower urinary tract. GSM does not only include genital and sexual symptoms, but also urinary symptoms such as dysuria, urgency, and recurrent urinary tract infections.

50% of postmenopausal women exhibited genitourinary disorders and 29% of those complained of urinary incontinence[5]. Other clinical manifestations are marked by vaginal, itching, dryness, and dyspareunia[6].

Recurrent infection was mostly a result of bacterial re-infection or persistence (relapse). Persistent infections are characterized by the non-eradication of the same bacteria in the urine even after a fortnight of sensitivity-adjusted treatment. Re-infection is defined as an infection with a different organism or the same organism, recurring after a fortnight. Recurrent uncomplicated urinary tract infection (UTI) is a common presentation to urologists and family doctors. Survey data suggest that 1 in 3 women will have had a diagnosed and treated UTI by age 24, and more than half will be affected in their lifetime. In a 6-month study of college-aged women, 27% of these UTIs were found to recur once and 3% a second time[7].

Urinary tract infections are the most common infection in postmenopausal women as mentioned earlier. It must be kept in mind that it is not the presence of microorganism that leads to urinary tract infection symptoms, but the expression of organism virulence factors. This expression allows microorganism adherence to urethra and perineum followed by its movement into the bladder and capture of the urothelium that leads to the symptoms other than the inflammatory response[4].

Pathophysiology and Risk Factors

The uro-pathogenic bacteria may resist host defences, adhere, and grow causing infection of the urinary tract. Despite several antibacterial factors such as pH, osmolality, urea concentration, organic acids, urine salt content, urinary inhibitors to bacterial adherence (Tamm-Horsfall protein), low-molecular-weight oligosaccharides, bladder mucopolysaccharide, secretory IgA, and lactoferrin, some bacteria may colonize and cause infection[8,9].

Gram negative bacteria such as- E. coli and Klebsiella spp. have been reported as the most common UTI causing organisms[10, 11, 8, 12, 13, 14]. E. coli causes around 70-95% of upper and lower UTI[15].

E. coli is the cause of 80–85% of community-acquired UTI, while Staphylococcus saprophyticus accounts for 5–10% urinary tract infections[16]. In very rare cases, UTI is caused by viral or fungal infections[12].

It has been demonstrated in various studies that women susceptible to UTIs have epithelial cells, equipped with additional receptors for drawing uropathogenic bacteria, compared with the controls[2, 15, 17]. Generally, UTI caused by E. coli is increasing at an alarming rate due to resistant strains[10]. According to Behzadi *et al*.[8], uropathogenic E. coli was the most commonly found bacteria across seasons during a 2-year study period. There is a significant association between female gender and urinary tract infection caused by E.coli ($p< 0.05$) calculated using χ^2 test. Klebsiella pneumoniae is found to be the second most common uropathogenic agent[8]. Gram negative bacteria of E. coli and K. pneumonia are the bacterial agents which invariably cause UTI, according to various studies[10] Streptococcus spp, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Enterococci were the third pathogens to cause urinary tract infection. Presence of coliforms and Enterococcus spp. in high numbers on the perineum may be a reason for the occurrence of UTI[8].

Epidemiologically, around 15%- 20% of women that are 65-70 years old, and 20%-50% of women over 80 years old suffer from bacteriuria[18] (asymptomatic bacteriuria or symptomatic). More often, bacteriuria occurs in functionally impaired women. Persistent bacteriuria occurs in nursing home residents, and transient bacteriuria occurs in young and healthy postmenopausal women. Bacteriuria is asymptomatic in the majority of elderly women and their treatment with antibiotics is not recommended[19].

It is estimated that the incidence of UTI in postmenopausal women ranges from 4%-15%. The clinical presentation of UTI is different in postmenopausal elderly women compared with younger women. Symptoms such as frequency, dysuria, hematuria, and fever are not reported by postmenopausal women, but they are likely to report flank pain.

Elements of risk associated with symptomatic UTI in postmenopausal women are poorly described; a previous history of UTI is considered as a major risk factor[20].

Other risk factors are mechanical or physiologic factors that affect bladder emptying, such as cystoceles[15], urinary incontinence, large post void residual volumes, atrophic vaginitis, and a history of urinary tract infection prior to menopause.

Postmenopausal women are also affected by recurrent UTI, which is defined as ≥3 UTI per year or ≥2 urinary tract infection per half year[21]. Among women, there are three categories of recurrent UTI. They are classified according to age as: 1) premenopausal women, 2) postmenopausal women in the age group of 50-70 years, who are neither institutionalized nor catheterized, and 3) elderly institutionalized women, who may be catheterized[18].

Jackson *et al.*[22] conducted a prospective cohort study in 1017 postmenopausal women aged 55 to 75 years to describe the incidence of and risk factors associated with UTI after menopause. Insulin treated diabetes is a potential risk factor for incident acute cystitis among postmenopausal women, while a lifetime history of UTI was the strongest predictor. The aging process in postmenopausal women contributes to occurrence of issues in lower urogenital tissue that also includes UTI[23].

In a case-control study by Raz *et al*.[18], 49 postmenopausal women with a history of

repeated occurrence of UTI were compared with 53 women with no history of UTI. The risk factors in healthy non-institutionalized and non-catheterized women were observed.

Jackson *et al.*[22] explained incidence as well as risk factors for acute cystitis among diabetic and non-diabetic postmenopausal women in a similar way. The effect of estrogen on these women was also discussed. The incidence of urinary tract infection was 0.07 people per year. The history of occurrence of kidney stones was associated with urinary tract infection at a borderline level[18].

In older institutionalized women, the major concerns associated with UTI were urine catheterization and functional status deterioration. Catheterization increases the possibility of infection in urinary tract[18].

Management and Treatment

The therapeutic role of oral Hormonal replacement therapy (HRT) has also been widely used by gynecologists and urologists for a variety of lower urinary tract symptoms, including urge and stress incontinence and recurrent UTIs. Estrogen alone was the dominant hormone until the increased risk of endometrial cancer led to the addition of progestins for women with an intact uterus. From the mid-1980s on, combined estrogen/progestin use steadily increased until approximately 38% of postmenopausal women in the United States used HRT. In the year 2000, 46 million prescriptions were written for Premarin (conjugated estrogens), making it the second most frequently prescribed medication in the United States[24].

The Women's Health Initiative (WHI) is the first randomized, primary prevention trial of postmenopausal women using hormones. What made this study headline news is that the Data and Safety Monitoring Board (DSMB) of the National Institutes of Health terminated the part of the study that compared estrogen/progestin with placebo early. The DSMB recommended stopping the trial because women receiving the active drug had an increased risk of invasive breast cancer, and an overall measure suggested that the treatment was causing more harm than good. However, topical oestrogen therapy in postmenopausal women lowers intravaginal pH, allowing increase in lactobacilli colonization that replaces the more pathogenic Gram-negative organisms[25, 26].

Prevalence of UTI among women administered vaginal estriol decreased to 0.5 episodes per year in comparison with 5.9 episodes per year in women receiving placebo; after 1 month of treatment lactobacillus appeared. The vaginal pH was also reduced from 5.5±0.7 prior treatment to 3.6±1.0 post treatment. Additionally, 45% of women administered estradiol were still free of UTI, while only 20% women treated with placebo were still free of UTI[27]. Currently, estrogen is mainly recommended for women in the postmenopausal stage, specifically for those afflicted with multidrug-resistant uropathogens, and among those whose symptoms are linked to atrophic vaginitis[28].

Kaisan *et al.*[29] studied prophylactic potential of the use of estriol in the treatment of urinary infections in postmenopausal women suffering from type 2 diabetes mellitus (DM) and asymptomatic bacteriuria. They observed that the administration of the local estriol can effectively prevent and treat UTI in postmenopausal females

In a case-control study by Foxman *et al.*[30],

the part played by health behaviour and sexual and medical history in healthy women between the ages of 40 to 65, with regard to UTI risk, was investigated. It was noticed that sexual activity was not linked with UTI acquisition in the group, while UTI history in the past year, exposure to cold, use of antibiotics in the previous two weeks, and urine loss were positively associated with UTI incidence[18].

After multivariable adjustment, sexual activity, parity, post-coital urination, post void residual bladder, urinary incontinence, vaginal dryness, vaginal bacterial flora, use of cranberry juice were not associated with increased incidence of acute cystitis[18].

In patients with recurrent urinary tract infection, oral or parenteral immune-prophylaxis is an additional option. Specific plant combinations, cranberry products, or probiotics may also be used[21].

The findings of the Cochrane Collaboration support the potential use of cranberry products in the prophylaxis of recurrent UTIs in young and middle-aged women. However, in light of the heterogeneity of clinical study designs and the lack of consensus regarding the dosage regimen and formulation to use, cranberry products cannot be recommended for the prophylaxis of recurrent UTIs at this time[31].

The other promising modalities include phyto-therapeutics, urine acidification, and use of mannose which influences bacterial intestinal and vaginal flora[29].

Antimicrobial prophylaxis has proved effective in reducing the risk of recurrent UTIs in women with two episodes of infection in the previous year. Continuous prophylaxis for six to 12 months reduces the rate of UTIs during the prophylaxis period, with no difference between the six-month and 12-month treatment groups after cessation of prophylaxis. Various dosages of prophylactic antibiotics have been suggested but no conclusive evidence supports the selection of a particular drug, dosage, or duration or schedule of treatment. The duration of prophylaxis should be guided by the severity of patient symptoms and by physician and patient preference. Six months of treatment, followed by observation for reinfection after discontinuing prophylaxis, has been empirically recommended[32]. Postcoital prophylaxis may be preferable in women with UTIs temporally related to intercourse. No marked difference in recurrent UTIs has been noted when using postcoital prophylaxis compared with daily prophylaxis[19], and depending on the frequency of sexual intercourse, postcoital prophylaxis usually results in less antibiotic use[33].

So in summary, continuous antibiotic prophylaxis or postcoital prophylaxis is most effective in recurrent UTI prevention. First line drugs available for the treatment of UTI are nitrofurantoin, trimethoprim, and fosfomycin trometamol [table 1]. The frequency of recurrent UTI can be reduced by 90%.

Turner *et al.*[34] demonstrated the sensitivity of dipstick urinalysis in postmenopausal women with irritative bladder symptoms. Palou *et al*.[35] conducted a multicenter, randomized, prospective and controlled study between two short antibiotic regimes: fosfomycin trometamol and ciprofloxacin in terms of eradication of bacteria in postmenopausal women with uncomplicated acute cystitis who complete the full course of antibiotic treatment. The fosfomycin trometamol and ciprofloxacin have a comparable efficacy profile in

postmenopausal women for the treatment of lower tract urinary infection.

Raz and Rozenfeld[36], in their research on women in the postmenopausal stage with uncomplicated UTI, reported that ofloxacin, 200mg once daily for 3 days[37] was more effective than a 7 day course of cephalexin, 500mg four times daily, in both short and long-term follow-up. Similar results were obtained in another study that included 183 postmenopausal women of 65 years of age with acute uncomplicated UTI treated with ciprofloxacin 250mg twice daily [18]. In another study, the bacterial eradication rate was high and the bacterial resistance rate to ciprofloxacin was low[38].

Antibiotics should not be used for the treatment of elderly women with asymptomatic bacteriuria [18]. The optimal antimicrobial dose and period of treatment in elderly women is similar to those suggested for young women[18].

Table 1. Available treatments for UTI in post-menopausal women

Authors, year	Study Type	Treatments	Indications
Ottawa, 2016	Review	Cranberry Products or Topical Estrogen-Based Therapy	UTI
Jansåker F., 2016	Randomized, double-blinded, placebo-control clinical trial	Pivmecillinam	Uncomplicated lower UTI
Palou *et al*., 2013	Multicenter, randomized, prospective and controlled study	Fosfomycin trometamol and ciprofloxacin	Eradication of bacteria in postmenopausal women
Reid et al, 2002	In vitro	Lactobacillus	Prevent uropathogen infection
McMurdo *et al*., 2009	Randomized controlled trial	Cranberry capsules with trimethoprim	UTI
Raz R.,1993	Controlled trial	Vaginal estriol	Restore vaginal flora, reduce pH, and reduce the number of symptomatic bacteriuria
Eriksen B., 1999	Randomized, open, parallel-group study	Estradiol-releasing vaginal rings	UTI
Raz and Rozenfeld, 1996	Clinical study	Ofloxacin, 200 mg once daily for 3 days	Uncomplicated UTI
Nygaard IE., 1996	Clinical study	3-day or a 7-day oral course of ciprofloxacin 250 mg two times daily	Acute uncomplicated UTI

Conclusion

The most prevalent bacterial infections present in the society and health care setting are the urinary tract infections. In spite of the increased incidence of bacteriuria among elderly women, the majority of research on urinary tract infection has been conducted on young women. Bacteriuria is very frequently observed in healthy postmenopausal women as well as institutionalized women. Bacteriuria in women of advanced age is linked with higher rates of mortality, but mostly it is asymptomatic and does not cause death. Estrogen deficiency may lead to the development of bacteriuria.

Multidrug-resistant uropathogens are growing at an alarming rate. Normal flora restoration with lactobacilli using probiotics is an alternative strategy. Another option may be competitive compound use, which inhibits bacteria attachment to the uroepithelium. However, neither of the two methods has reported any results which could be termed as conclusive. Proanthocyanidin is present in cranberries which could prevent E. coli uropathogen colonization in the vaginal mucosa, and decrease bacteriuria frequency.

There is a relation between bacteriuria on one side and diabetes and sexual intercourse on the other side. The role of estrogen (vaginal or oral) along with probiotics and lactobacilli use continues to remain questionable. Further randomized studies on a large scale are required to define as well as ascertain the explicit function of estrogen therapy, lactobacilli, probiotics, and other techniques to reduce the use of antibiotics.

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النساء بعد سن اليأس والتهابات المجاري البولية: مراجعة علمية

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الملخص

ان التهابات المجاري البولية هو امر على درجة عالية من الاهمية عالميا، وهي تصيب النساء أكثر من الرجال حيث تتسبب بها البكتيريا البشرية الطبيعية التي تدخل الاحليل اما من الامعاء او المهبل او منطقة العانة. ان النساء بعد سن اليأس هن أكثر عرضة لأعراض التهابات المجاري البولية ويعزى ذلك بشكل رئيسي لانخفاض مستوى هرمون الاستروجين في الجسم. بينت دراسة اجراها الباحثان داسون وكابور ان نسبة حدوث التهابات المجاري البولية لمرة واحدة هي 27% ونسبة حدوثها بشكل متكرر هي 3%. وكانت اغلب حالات الالتهابات المتكررة ناتجة عن حدوث التهاب جديد او استمرار الالتهاب القديم. ان البكتيريا السلبية لصبغة غرام مثل الايشيريشيا كولاي ومجموعة الكلبسيلا هما الاسباب الاكثر شيوعا لالتهابات المجاري البولية. حيث ان الايشيريشيا كولاي مسؤولة لوحدها عن 70-95% من التهابات المجاري البولية السفلية والعلوية، كما انها مسؤولة ايضا عن 80-85% من التهابات المجاري البولية المكتسبة من المجتمع، بينما بكتيريا ستافيلوكوكس سابروفيدكس مسؤولة عن 5-10% وفي بعض الاحيان النادرة تكون الفيروسات والفطريات هي المسبب لالتهابات المجاري البولية. ان الاعراض السريرية لالتهابات المجاري البولية تختلف في السيدات بعد سن اليأس والسيدات المتقدمات في السن عنه عند السيدات الصغار في العمر، فالأعراض مثل تكرار الرغبة في التبول وحرقة البول والبيلة الدموية والحمى غير موجودة في السيدات المتقدمات في السن لكنهن يعانين كثيرا من الم في الخاصرة. كما انه من الشائع ان تعاني السيدات بعد سن اليأس من التهابات المجاري البولية المتكررة والذي يعرف بالإصابة بثلاثة التهابات او أكثر في العام الواحد او بإصابتين او أكثر خلال 6 شهور. ومن الجدير بالملاحظة، العلاقة الطردية بين نسبة الوفاة ونسبة حدوث البيلة الجرثومية عند السيدات المتقدمات في السن، مع العلم انه في اغلب الحالات تكون البيلة الجرثومية بدون اعراض ولا تسبب الوفاة. ان الهدف من هذه الورقة هو اجراء مراجعة علمية للتوصل الى فهم أفضل وبالتالي علاج أفضل لجميع جوانب التهابات المجاري البولية عند السيدات المتقدمات في السن.

الكلمات الدالة: التهابات المجاري البولية، البيلة الجرثومية، الاستروجين، النساء بعد سن اليأس، المضادات الحيوية الوقائية، المعينات الحيوية لاكتوباسلاي.