CLINICAL VIGNETTE

Estrogen Repletion in Postmenopausal Women May Reduce Recurrent Urinary Tract Infections

Grace I. Chen, M.D. and Maija Sanna, M.D.

Case

An 83-year-old female with type 2 diabetes, hypertension, congestive heart failure, urinary incontinence, and recurrent urinary tract infections (UTIs) presented to Geriatrics to establish primary care. At the time of presentation, she was taking nitrofurantoin nightly for prophylaxis against recurrent UTIs. In addition to the nitrofurantoin, she rotated cefpodoxime, ciprofloxacin, and doxycycline prophylactically on a monthly basis per her prior primary care physician in an attempt to prevent recurrent UTIs. A urine culture obtained for dysuria on the day of presentation grew greater than 100,000 colonies of *Escherichia coli* (*E. coli*) that was resistant to all oral medications except for sulfamethoxazole/trimethoprim to which she has an allergy. Her prophylactic antibiotics were discontinued, and she was referred to urology to evaluate her chronic urinary incontinence and recurrent UTIs. The urologist started her on vaginal estradiol cream. Urine culture obtained two months after starting the vaginal estradiol cream grew two types of *E. coli* organisms, both of which were pan-sensitive to all antibiotics. Subsequent urine cultures for dysuria growing *E. coli* have all continued to remain pan-sensitive two years after starting estradiol vaginal cream. Although she continued to experience UTIs, the frequency of her infections was reduced.

Discussion

Urinary tract infections are one of the most common infections and women are particularly affected by recurrent UTIs.[1] Recurrent UTI's are defined as two or more infections in six months or three or more infections in one year. About half of all women experience at least one UTI during their lifetimes with more than 25% of these women experiencing a recurrence within six months.[1] The frequency of UTI's increases among postmenopausal women. Although the prevalence of UTI is less than 5% in young to middle aged women, approximately 15-20% of women 65- to 70-year old and 20-50% of women greater than 80-year-old[2] have bacteriuria.

Many UTIs are caused by *E. coli*, which adheres to the bladder epithelium and rapidly invades the superficial umbrella cells lining the bladder lumen. The bacteria then multiply and form intracellular bacterial aggregates, which lead to an infection. These aggregates may then invade another cell and lie dormant as potential source for recurrent infections.

Both the distal vagina and urethra are rich in estrogen receptors. In premenopausal women, estrogen influences the acidity of the vagina by the conversion of glucose to lactic acid by lactobacilli. This process prevents the overgrowth and colonization of *Enterobacteriaceae* in the vagina. In addition, in-vitro studies on vaginal-ectocervical epitheial cells have shown that estrogen upregulates active protein secretion that acidifies vaginal PH independent of lactobacilli.[3] The depletion of estrogen in postmenopausal state changes the milieu. Low estradiol levels after menopause have been linked to recurrent infections in elderly women due to atrophy of the vaginal and urothelial walls.

Studies have explored the role of exogenous estrogen in reversing the effects of estrogen depletion in post-menopausal women. A randomized, double-blind, placebo-controlled trial in 1993 showed that vaginal estrogen may prevent UTIs[4]. The incidence of UTI in the group given estriol was significantly reduced compared to placebo, 0.5 episodes per year versus 5.9 episodes per year. In addition, lactobacilli reappeared after one month in 61% of the estriol-treated women but in none of the women receiving placebo. The mean vaginal pH also declined in the estriol group and vaginal colonization with *Enterobacteriaceae* fell significantly in the estriol group. Similar results were obtained using an estradiol-vaginal ring with 45% of the women remaining UTI free compared to 20% of the placebo group after 36 weeks.[5] However, other studies that have shown contradictory findings.[6] Thus, the literature remains inconclusive on effectiveness of vaginal estrogen in preventing recurrent UTIs in postmenopausal women.

The literature also remains sparse on the exact mechanism(s) by which estrogen repletion in menopause may reduce recurrent UTIs. Research using human urothelial cells and a mouse model supports the idea that estrogen modulates two epithelial defense mechanisms.[7] One mechanism is inducing the expression of antimicrobial peptides, which enhances the urothelium's ability to restrict bacterial multiplication. Another mechanism is that estrogen promotes the expression and redistribution of cell-cell contact in associated proteins, which strengthens the integrity of the epithelium and prevents excessive loss of the superficial cells during the infection. Both of these mechanisms may prevent bacteria from reaching the deeper layers and prevent them from developing reservoirs that can serve as a source for recurrent infections.

Furthermore, the strengthening of the defense mechanisms possibly prevents the resistant strains of *E. coli* from forming reservoirs and may even prevent resistant strains contributing to bacteriuria altogether. Replacement estrogen may also up regulate active protein secretion that acidifies vaginal PH as seen in intrinsic estrogen.

While the efficacy of estrogen in preventing recurrent UTIs in the postmenopausal woman remains questionable from the available literature, it is worthwhile from a clinical perspective to consider vaginal estrogen, especially in those with multidrug-resistant uropathogens. UTIs with these multidrug-resistant uropathogens limit the options and efficacy of anti-microbial prophylaxis and treatment. These infections in particular cause substantial costs to the health care system. It is also worthwhile to note that excessive use of prophylactic antibiotics can also increase resistance patterns.

Although the patient in the case still gets recurrent UTIs, the frequency has decreased since initiating topical vaginal estrogen, and more importantly, she has been able to be treated on an outpatient basis with oral antibiotics, eliminating the need for parenteral antibiotics.

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