

Hormone Replacement Therapy or Prophylaxis in Postmenopausal Women with Recurrent Urinary Tract Infection

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Urinary tract infection (UTI) is the most common bacterial infection in women, and it occurs with much greater frequency among elderly than among younger women and with increasing frequency among postmenopausal women. In young to middle-age women, the prevalence of UTI is <5%, rising considerably with advancing age. Epidemiologic studies have shown that ~15%–20% of 65- to 70-year-old women have bacteriuria, compared with ~20%–50% of women >80 years old [1].

Despite the high prevalence of bacteriuria among postmenopausal women, the factors predisposing such women to UTI have not been explored adequately as compared with those for premenopausal women. However, it has been shown in an epidemiologic and clinical case-control study that nonsecretory status and urologic factors, such as residual volume, reduced urinary flow, previous urogenital surgery, incontinence, and cystocele, are strongly associated with recurrent UTIs in postmenopausal women [2]. Another important factor related to recurrent UTIs is the lack of estrogen, which occurs during menopause, the period starting 1 year after the last menstruation and a time that is expected to encompass one-third of a woman's life.

Current Knowledge

Estrogen and the urogenital tract Naturally occurring estrogens are 18-carbon steroids characterized by an aromatic A ring. The principle estrogen secreted by the ovary is estradiol, and it is also the most potent estrogen. Estrone is also secreted by the ovary, but most is formed by extraglandular conversion of androstenedione in peripheral tissues. Although levels remain stable after menopause, the amount is insufficient to maintain premenopausal circulating levels of estrogen. Estriol, the main estrogen in urine, arises from the hydroxylation of estrone and estradiol [3].

The distal vagina and urethra share a common embryologic origin and are subject to similar hormonal influences, both being richly supplied with estrogen receptors. Estrogen receptors in the lower urinary tract have been identified in the trigonal area, the epithelium lining of the urethra, and the vascular complex in the urethra submucosa. In premenopausal women,

estrogen influences the acidic pH of the vagina. This acidic vaginal environment is a result of the conversion of glucose to lactic acid by lactobacilli [3], a process that prevents the overgrowth and colonization of Enterobacteriaceae in the vagina. After menopause, the vagina is characterized by different degrees of atrophy, clinically manifested as a syndrome consisting mainly of vaginal dryness, itching, irritation, and dyspareunia; recurrent UTIs and urinary incontinence are also disabling postmenopausal conditions [4]. More than 50% of women ≥60 years old have some degree of urogenital symptoms.

Exogenous estrogen restores these urogenital changes and clinical symptoms. However, the treatment of these complaints requires an estrogen with specific urogenital activity without producing endometrial proliferation [4]. Although medium-potency estrogens, mainly estradiol and conjugated estrogens, clearly alleviate urogenital symptoms related to menopause, benefits may also be achieved by the use of low-potency estrogen formulations administered orally (estriol) or intravaginally (estriol, dienestrol, or estradiol in very low doses).

Ethinylestradiol, which is present in most oral contraceptive pills, and the so-called conjugated estrogens are classified as high-potency substances, having a slow metabolism and a long-lasting effect. Estriol is a metabolic end product with a short retention time of the nuclear estrogen receptor in different target tissues. It is classified as a low-potency estrogen and has a specific urogenital activity. While estradiol and estrone bind equally strongly to endometrial and vaginal estrogen receptors, estriol binds selectively to vaginal and marginally to endometrial receptors. Therefore, estradiol and estrone induce endometrial proliferation, increasing the risk of endometrial carcinoma, and when they are prescribed, it is necessary to add cyclic progesterone to counteract the action of estrogen on the endometrium. Women receiving these hormones will have vaginal bleeding. However, the use of estriol does not induce endometrial proliferation and, therefore, the use of progesterone is not necessary. In addition, because estriol is an end product, its administration does not influence the level of other estrogens. Estriol can be given orally or locally via vaginal cream or pessaries. Peak levels of estriol are lower when administered orally rather than vaginally due to the first-pass effect of the liver.

Estrogen therapy in the prevention of recurrent UTI Atrophy of the urethral epithelium and the trigonal area in the bladder and some degree of urge incontinence can also be alleviated with vaginal estrogen. Kicovic et al [5] showed that vaginal estriol is efficient and safe for treatment of postmenopausal atrophic vaginitis and associated complaints. In addi-

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Indications	
<u>Oral Therapy</u> - Young postmenopausal women	<u>Advantages</u> - Avoid menopausal symptoms - Prevent osteoporosis - Prevent ischemic heart disease - Prevent UTI
<u>Vaginal Therapy</u> - Women >60 years old	<u>Advantages</u> - Improve symptoms related to atrophic vaginitis - Improve urge incontinence - Prevent UTI
Contraindications	
<u>Absolute</u> - Endometrial carcinoma - Breast carcinoma - Thromboembolic disorders - Liver disease	<u>Relative</u> - High blood pressure? - Diabetes mellitus? - Gall stones?
Difficulties in vaginal therapy	
<u>Physical Limitations</u> - Tremor - Obesity - Status after cerebrovascular accident - Dementia - Psychological problems - Education/cultural behavior	

Figure 1. Indications and contraindications for estrogen therapy UTI, urinary tract infection

tion, several small studies have shown that small doses of oral estradiol reduced the incidence of UTI in postmenopausal women [6].

In 1993, it was demonstrated in a randomized, double-blind, placebo-control study, that vaginal estradiol treatment had a dramatic effect on the incidence of recurrent UTIs in postmenopausal women [7]. In the study, it was shown that the incidence of UTI in women who received vaginal estradiol was reduced to 0.5 episodes per year, compared with 5.9 episodes per year in women treated with placebo. In addition, after 1 month of treatment, lactobacillus appeared in 60% of the estrogen-treated group but in none of those in the placebo group, and vaginal pH decreased from 5.5 ± 0.7 before treatment to 3.6 ± 1.0 after treatment.

In 1999, similar results were presented by Eriksen [8], using an estradiol-releasing vaginal ring. In that study, the women in the estradiol group had a considerable reduction in the frequency of urogenital symptoms, such as vaginal dryness, dyspareunia, and urge and stress incontinence, and after 36 weeks of study, 45% of the women receiving estradiol remained free of UTI, in contrast to 20% of the women treated with placebo. Vaginal pH was also reduced by the local estrogen therapy. Maloney [9] also showed that topical replacement of vaginal

estrogen in female nursing-home inhabitants reduced urogenital symptoms, vaginal pH, and the number of new episodes of UTI.

In conclusion, estrogen replacement is effective not only in the treatment of urogynecological symptoms related to menopause but also in the prevention of recurrent UTIs. Younger postmenopausal women can benefit from oral hormonal therapy, which improves clinical symptoms related to menopause and helps avoid osteoporosis and ischemic heart disease, the use of vaginal estrogen should be limited to women ≥ 60 years old for the treatment of atrophic vaginitis, recurrent UTIs, and urge incontinence.

Indications and contraindications for estrogen therapy Figure 1 summarizes the indications and contraindications for estrogen therapy. The contraindications for the use of hormone replacement therapy (HRT), including cardiovascular diseases, diabetes, liver disease, otosclerosis, endometriosis, melanoma, and hormone-dependent tumors, had been taken from the data sheets of oral contraceptives, and oral contraceptives are derived from alkyllestrogens, which are very different from the esterized or micronized estrogen used in HRT. In other words, to my knowledge, no data regarding the risks associated with the use of HRT in postmenopausal women have been recorded.

However, the use of HRT, including vaginal therapy, is absolutely contraindicated in women with active venous thromboembolism, severe active liver disease, and endometrial and breast carcinoma but can be administered to women with diabetes, gallstones, and other relative contraindications.

New studies are needed to define the safety of HRT and especially the use of estriol or other low-potency estrogens. In addition, other aspects need to be considered before the route of estrogen therapy is chosen. For instance, physical limitations related to cultural behaviors can limit the use of vaginal therapy

Commentary

Questions and concerns regarding estrogen therapy Two questions have been raised regarding the use of prolonged estrogen therapy in the prevention of UTI in postmenopausal women. First, what is the potential carcinogenic effect of estrogen? Second, can estrogen therapy replace prolonged antimicrobial chemoprophylaxis, which is considered the reference standard in the prevention of UTI in women?

In addition, the efficacy and safety of oral versus vaginal estriol treatment must be determined. Estriol, has been used for more than 4 decades and has been regarded as an estrogen that does not cause endometrial cancer. However, Weiderpass et al. [10] showed in an epidemiologic case-control study that oral but not vaginal treatment with estriol increased the relative risk of endometrial proliferation and carcinoma. The authors speculate about a possible explanation of this phenomenon; however, they did not find a reason for the increase of endometrial hyperplasia and carcinoma in women receiving oral estriol, and they suggested that oral estriol therapy must be combined with a progestagen preparation.

The efficacy and safety of estriol compared with prolonged antimicrobial chemoprophylaxis in postmenopausal women with recurrent UTIs, was recently assessed in a double-blind

dummy comparative study, in which 200 women received vaginal estriol twice weekly or macrocrystals of nitrofurantoin daily during 9 months. The results and conclusions are not yet complete and will be published in the near future.

Conclusions Low-potency estrogens have been shown to be effective not only in the improvement of urogenital complaints related to estrogen deficiency but also in the prevention of recurrent UTI in postmenopausal women. The safety and the comparative efficacy of both oral and vaginal estriol should be evaluated in future studies.

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