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 ureologic factors, such as residual volume, reduced urinary flow, previous urologic 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 lactate 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 (estrol) or intravaginally (estrol, dienestrol, or estradiol in very low doses).

Ethinyloestradiol, 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. Estrol 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, estradiol binds selectively to vaginal and marginally to endometrial receptors. Therefore, estradiol and estrone induce endometrial proliferation, increasing the risk of endometrial carcinoma. 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 estrol does not induce endometrial proliferation, and therefore, the use of progesterone is not necessary. In addition, because estrol is an end product, its administration does not influence the level of other estrogens. Estrol can be given orally or locally via vaginal cream or pessaries. Peak levels of estrol 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. Kacic et al. [5] showed that vaginal estrol is efficient and safe for treatment of postmenopausal atrophic vaginitis and associated complaints. In addi-
Indications

Oral Therapy
- Young postmenopausal women

Advantages
- Avoid menopausal symptoms
- Prevent osteoporosis
- Prevent ischemic heart disease
- Prevent UTI

Vaginal Therapy
- Women >60 years old

Advantages
- Improve symptoms related to atrophic vaginitis
- Improve urge incontinence
- Prevent UTI

Contraindications

Absolute
- Endometrial carcinoma
- Breast carcinoma
- Thromboembolic disorders
- Liver disease

Relative
- High blood pressure?
- Diabetes mellitus?
- Gallstone?

Difficulties in vaginal therapy

Physical Limitations
- Tremor
- Obesity
- Status after cerebrovascular accident
- Dementia
- Psychological problems
- Education/cultural behavior

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

dummy comparative study, in which 200 women received vaginal estrol twice weekly or macrocrystals of methyluracil 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 urinogenital 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 estrol should be evaluated in future studies.

References