Estrogens and Urinary-Tract Infection

Walter E. Stamm
University of Washington School of Medicine, Division of Allergy and Infectious Disease, Seattle

(See the article by Curran et al., on pages 680–3.)

The effects of estrogen on the risk of urinary-tract infection (UTI) in women has been the subject of many studies in both humans and experimental animals. Often, these studies have come to seemingly contradictory results: some have suggested an increased risk attributable to estrogen and others that estrogens may be preventative. In part, this confusion arises because the physiological effects of estrogen on different anatomic parts of the urinary tract differ depending on the specific effect and the outcome measured. For example, in the absence of estrogen, the periurethral and vaginal microflora, which is usually predominated by hydrogen peroxide–producing lactobacilli and few Escherichia coli, changes dramatically to a flora with few or no lactobacilli but many E. coli [1]. This change in flora is associated with a markedly increased risk of recurrent E. coli bladder infections. In a randomized, placebo-controlled trial of topical intravaginal estrogen cream in such women, both the reestablishment of the normal lactobacillus-dominant vaginal flora and reduced rates of UTI were demonstrated in estrogen-treated women [2]. However, topical vaginal estrogen also reverses the atrophic vaginitis that accompanies menopause, making sexual intercourse more comfortable and likely more frequent in users. Because sexual intercourse is itself a risk factor for UTI in women [3], this effect may counter the beneficial effects of normalizing flora. Animal models have not been used much to study these particular aspects of estrogen-related susceptibility to UTI, because both the urogenital anatomy and normal flora in small animals differ considerably from those of women. Thus, the preventive effects of estrogen replacement on UTI observed in postmenopausal women, which is thought to be mediated by changes in vaginal flora, are not usually seen in animal studies. As in the study by Curran et al. in this issue of the Journal of Infectious Diseases [4], most animals are in fact inoculated via urethral catheterization in models of experimental infection, which completely bypasses the stage of infection in which the vaginal microbial flora plays an important role.

On the other hand, the study by Curran et al. suggests that the greatest effect of estrogen in their model was at the other end of the urinary tract—namely, the kidney. They demonstrated an increased microbial burden in the kidneys among estrogen-treated mice, regardless of the adhesin type (type 1, P, or Dr) or the E. coli strain used. Interestingly, there was not a significant effect of estrogen on the risk or intensity of bladder infection; thus, the main effect of estrogen seemed to be in facilitating upper-urinary-tract infection. In their model, the results were not associated with the Toll-like receptor 4 background of the mouse. As is pointed out by the authors, the effects of estrogen on the anatomy and physiology of the mouse urinary tract were not studied, but such factors could be responsible for facilitating upper-urinary-tract infection. In humans and in other animal studies, for example, hormonal changes, including hyperestrogenism, promote bladder atony, ureteral dilatation, and reduced ureteral peristalsis, all of which facilitate the migration of bacteria from the bladder to the kidney [5]. Similar physiological changes in the mouse, if present, might explain the markedly enhanced risk of pyelonephritis in estrogen-treated mice reported by Curran et al. Estrogen-mediated alterations of host defense mechanisms in the kidney could also be responsible for the authors’ observations and would seem to be another important research direction.

From a clinical perspective, the only currently recommended use of estrogens for prevention of UTI is in postmenopausal women who are not receiving oral estrogen but are having ≥3 recurrent UTIs per year. Topical vaginal estrogen preparations have been demonstrated to be effective in such women [1, 2], and they may be a particularly useful alternative when antimicrobial resistance to multiple drugs limits the options and effectiveness of antimicrobial prophylaxis.
References