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Original Article

Does the Menopause Influence the Risk of Bacteriuria?

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Abstract: The objective of this study was to test the hypothesis that the risk of bacteriuria is increased as a result of estrogen deprivation following the menopause. All midstream urine samples (MSU) sent to the King's College Hospital department of microbiology by general practitioners in 1997 were assessed. Bacteriuria was diagnosed when the bacterial count was $>10^5$ organisms/ml. Logistic regression analysis was performed to investigate the effects of age and sex on the likelihood of having a positive result. Non-linear effects of age were investigated, with interest focusing in particlar on the time around the menopause. There were 15 392 MSU samples analyzed; 11 811 (77%) were from women and 3581 (23%) from men. In both sexes the proportion of positive results increased with increasing age ($P<0.0001$). The specimens taken from women were significantly more likely to be positive than those taken from a man of the same age ($P<0.0001$). In women there was no evidence of any non-linear relationship between age and the log odds of a positive result. A plot of the proportion of positive results versus age did not suggest any departure from a linear relationship at or following the menopause. In conclusion, the increased risk of bacteriuria which occurs as women get older appears to happen gradually as a result of the aging process, rather than as the result of pathophysiological changes in the urogenital tract that take place at or following the menopause.

Keywords: Estrogen; Menopause; Urinary tract infection

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Introduction

Urinary tract infections (UTI) occur in women of all ages, with at least 20%–30% of the female population being affected at some time [1]. Risk factors include sexual intercourse, the use of the diaphragm for contraception, previous urinary tract infection, and lower urinary tract dysfunction such as ureteric reflux or impaired bladder emptying [2]. Elderly women are thought to be particularly likely to develop bacteriuria, with a reported prevalence of 20% in community-dwelling women and sometimes over 50% in institutionalized patients [3,4]. However, it is at present unclear if the increased risk of UTI which occurs as women get older is a result of the aging process or of the pathophysiological changes that occur in the urogenital tract as a result of estrogen deficiency following the menopause.

Materials and Methods

All midstream urine samples (MSU) sent from the community by general practitioners (GP) in 1997 were assessed. The indication for urine culture was determined on an individual basis and therefore not available for analysis. Bacteriuria was diagnosed when the urinary bacterial count was $>10^5$ organisms/ml. Samples with a mixed growth of organisms were classified as not infected, in line with departmental policy. Each result was entered on to a computerized database which included details of the patient's age, sex, and the infecting organism. Logistic regression analysis was performed to investigate the relationship between age and the likelihood of having a positive (infected) MSU result, and to compare the results for men and for women. Changes in the rate of bacteriuria occurring at

around the time of the menopause were investigated by looking for a non-linear (more specifically, a quadratic) relationship between age and the log odds of a positive result. Among positive MSU results from female subjects, the proportions due to particular infecting organisms were analyzed in the same way to try and establish if the menopause led to a change in the bacterial flora of infected urine.

Results

All 15 392 MSU samples sent from the community-based general practices from 1 January 97 to 31 December 97 inclusive were analyzed; 11 811 (77%) were from women and 3581 (23%) from men. The number of samples sent from patients in each age group is shown in Fig. 1. A logistic regression analysis looking

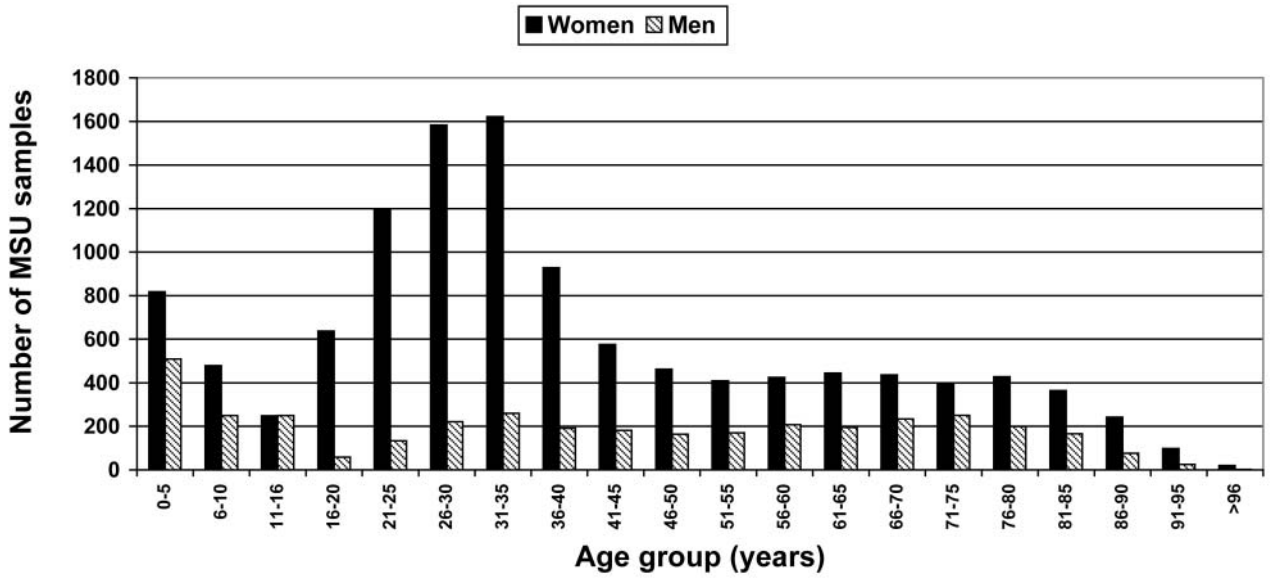

Fig. 1. The number of urine samples sent from patients in each age group.

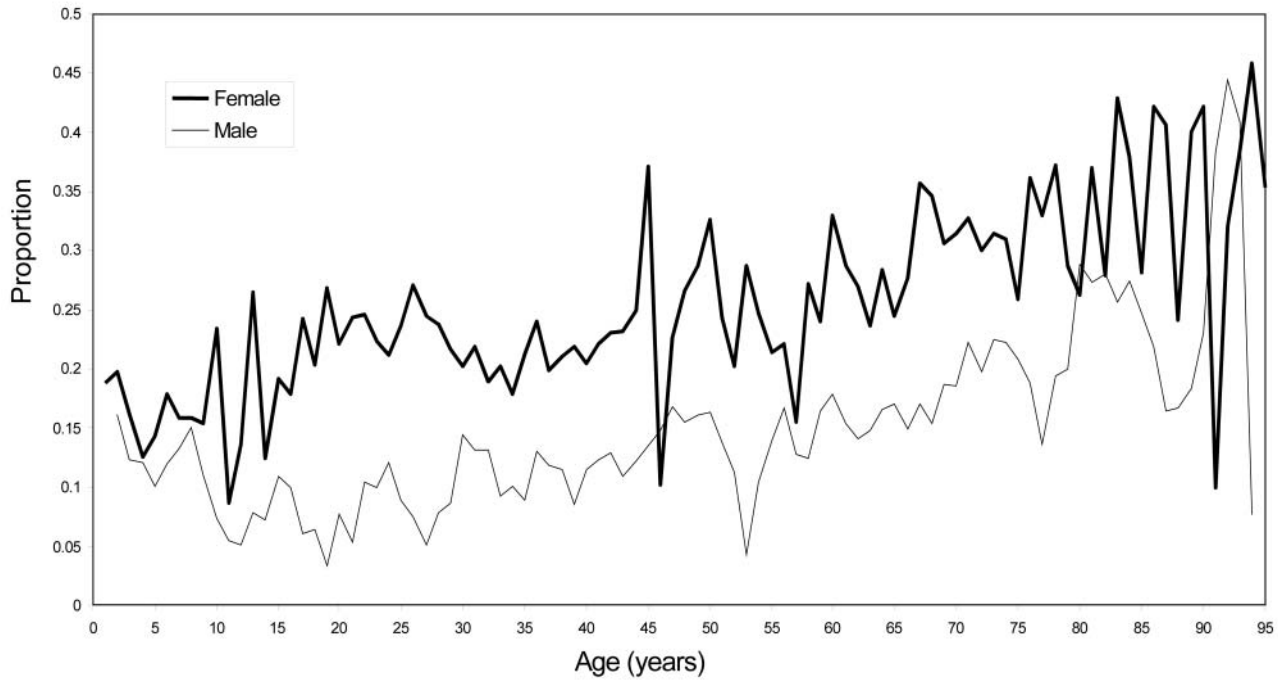

Fig. 2. Proportion of samples that were positive, by subject's age. The proportions for females are calculated and plotted at each year of age. For males, from whom there were fewer samples, the proportion plotted at a given age is calculated over a 3-year interval around that age.

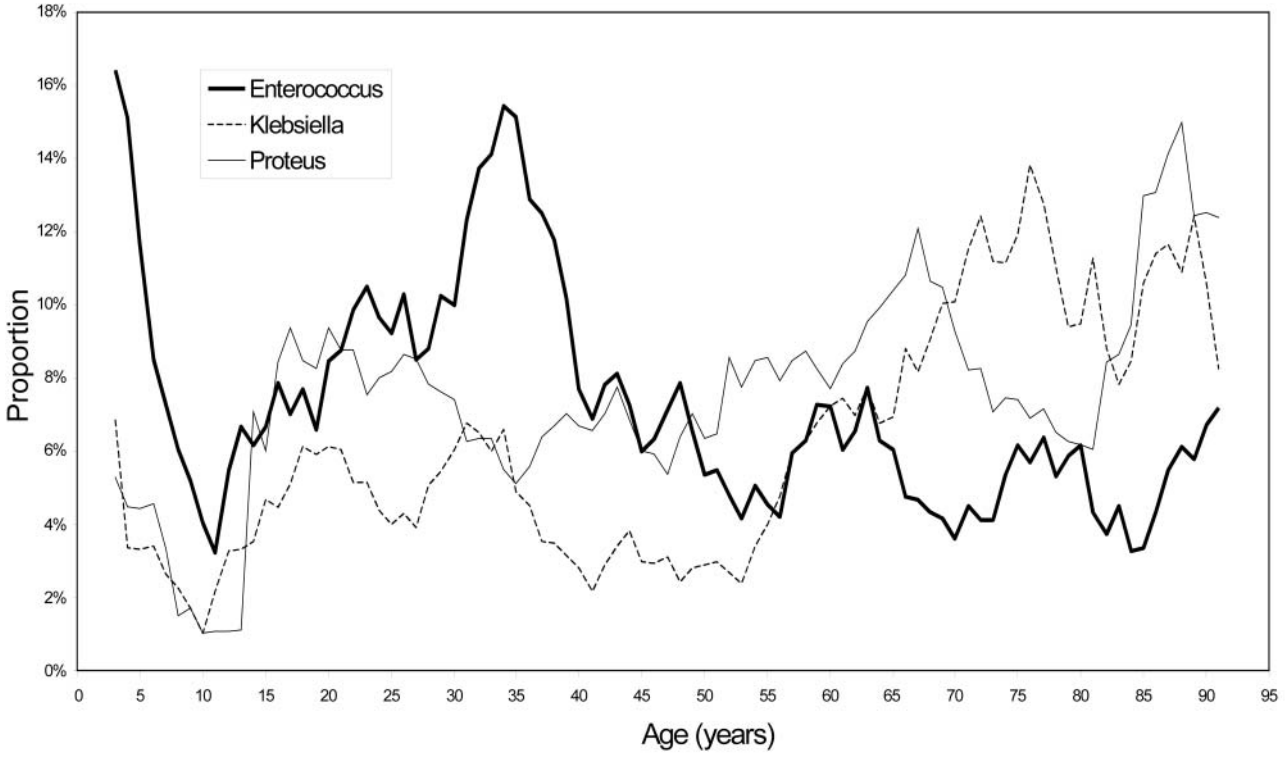

Fig. 3. Proportions of the more common organisms in positive samples from female subjects. The proportion plotted at a given age is calculated over a 7-year age interval around that age. 69% of infections were caused by *E. coli*, and this proportion did not change significantly with age. This has been left off the graph in order to allow increased resolution at proportions below 20%.

at the effects of age and sex found a significant linear effect of age ($\chi^2 = 179.4$, $P<0.0001$) which did not differ between males and females (interaction $\chi^2 = 0.02$, $P=0.88$). However, there was a significant main effect of sex ($\chi^2 = 170.9$, $P<0.0001$): a specimen from a woman was more likely to be positive than one from a man of the same age (Fig. 2).

However, when non-linear effects of age were also considered they were found to differ between men and women (interaction $\chi^2 = 8.95$, $P=0.003$). In women, there was no evidence of any non-linear relationship between age and the log odds of a positive result ($\chi^2 = 0.79$, $P=0.37$). A plot of the proportion of positive results did not suggest any departure from a linear relationship at or following the menopause. In men there was a significant non-linear relationship between age and the log odds of a positive result ($\chi^2 = 14.4$, $P=0.0001$). Over the first 15–20 years of life the proportion of positive MSU results fell steadily, but thereafter increased with age.

The organisms that led to positive MSU results in women were then investigated. *Escherichia coli* was the most common overall, accounting for 69.0% of infections. *Enterococcus* accounted for 8.5%, *Proteus* for 7.6% and *Klebsiella* for 6.1%. No other genus accounted for more than 2% of infections.The proportions of each of *E. coli*, *Enterococcus*, *Proteus* and *Klebsiella* in positive results from women were analyzed using logistic regression to fit a quadratic relationship between age and the log odds. If the quadratic term was not significant, a linear relationship was tried instead. The only organism for which the quadratic term approached significance was *Klebsiella* ($\chi^2 = 3.60$, $P=0.058$), which appeared to account for a constant proportion of infections at ages below 50, and a steadily increasing proportion as age increased above 50 (Fig. 3). The proportion of infections caused by *Enterococcus* decreased with increasing age ($\chi^2 = 28.0$, $P<0.0001$), whereas *Proteus* was responsible for a steadily increasing proportion of infections ($\chi^2 = 6.89$, $P=0.009$) (Fig. 2). The proportion of positive results due to *E. coli* did not vary with age ($\chi^2 = 1.28$, $P=0.26$).

Discussion

The female lower urinary and genital tracts have a common embryological origin, both arising from the primitive urogenital sinus. Estrogen receptors have been located in the vagina, urethra and trigone of the bladder in areas that have undergone squamous metaplasia [5,6]. The urogenital tract is therefore sensitive to fluctuations in the circulating level of sex steroids. Estrogen levels fall following the menopause, and as a result changes in the vaginal flora occur which are thought to place women at an increased risk of bacteriuria. There is a decrease in vaginal pH, a reduction in the number of lactobacilli and an increase in colonization by fecal

Table 1. Randomized studies of oestrogen for recurrent urinary tract infection

Study	Study group	Type of estrogen	Route of delivery	Duration of therapy	Results
Kjaergaard et al. 1990	21 postmenopausal women with recurrent cystitis 10 active group 11 placebo	Estradiol	Vaginal tablets	5 months	Number of positive cultures not statistically different between the two groups.
Kirkengen et al. 1992	40 postmenopausal women with recurrent UTIs 20 active group 20 placebo	Estriol	Oral	12 weeks	Both estriol and placebo significantly reduced the incidence of UTIs ($P<0.05$). After 12 weeks oestriol was significantly more effective than placebo ($P<0.05$)
Raz & Stamm 1993	93 postmenopausal women with recurrent UTIs 50 active group 43 placebo	Estriol	Vaginal cream	8 months	Significant reduction in the incidence of UTIs in the group given estriol compared to placebo ($P<0.001$).
Cardozo et al . 1998	72 postmenopausal women with recurrent UTIs 36 active group 36 placebo	Estriol	Oral	6-month treatment period with a further 6 months' follow-up	Reduction in urinary symptoms and incidence of UTIs in both groups. Estriol no better than placebo
Eriksen 1999	108 women with recurrent UTIs 53 active group 55 no treatment	Estradiol	Estring	36 weeks for the active group 36 weeks or until first recurrence for the controls	Cumulative likelihood of remaining free of infection was 45% in active group and 20% in control group ($P=0.008$)

uropathogens [7]. For this reason, exogenous estrogen has been administered both orally and topically to try and reverse these changes, with the aim of restoring the bacterial flora of the genital tract to the premenopausal state. However, the five published randomized studies of estrogen replacement for prophylaxis against recurrent urinary tract infections (summarized in Table 1) have given conflicting and largely disappointing results, with only two showing that estrogen is better than placebo when given for this indication [8–12]. Therefore, it is possible that women are at an increased risk of lower urinary tract infection as they get older because of the effects of aging, rather than because of the pathophysiological changes associated with the menopause and consequent estrogen deficiency.

There are a number of functional changes in the lower urinary tract which may place women at an increased risk of bacteriuria as they get older. Urodynamic studies have shown that the urethra and bladder become less efficient with age [13,14]. Elderly women have a reduced urine flow rate, increased urinary residual, a higher first sensation of a desire to void and increased bladder capacity, although the later may fall in the eighth and ninth decades [15]. In addition, detrusor pressures at urethral opening and closure during voiding fall in absolute terms as women become older [16]. Poor perineal hygiene also becomes more common because of an increased risk of urinary or fecal incontinence at a time when catheterization for a variety of reasons is more prevalent. There is little evidence to suggest that impairment of immune and inflammatory responses increases susceptibility to infection in elderly women, although there is some evidence that systemic responses to acute inflammatory stimuli may be dysregulated in old age [17].

If changes in the vaginal flora at or following the menopause were really responsible for the increased risk of bacteriuria as women get older, we would have expected to see an acceleration in the number of positive MSU results with increasing age, starting at the earliest ages of menopause (and, furthermore, this pattern would not have been repeated in male subjects). Instead, what we found was a steady rate of increase in positive MSU results from females (and indeed from males) from early adulthood onwards. The most common infecting organism was *E. coli*, which was present in 69% of infected samples from females and 49% of infected samples from males. The prevalence of *E. coli* and the other organisms shown in Fig. 2 was similar to that previously reported by Grüneberg [18]. There was in fact a fall in the proportion of positive results due to an Enterococcus with increasing age in our sample, suggesting that colonization of the vagina with bowel flora was not the main underlying cause for the increase in the rate of infection as women get older.

Longitudinally to determine the changes occurring perimenopausally in the vaginal and urinary flora of community-based women would require a large, expensive study of probably at least 10 years' duration. We therefore used the microbiological database at King's College Hospital as a model for the changes occurring in the population. There are of course some limitations to this approach, which have been recognized. These data are cross-sectional rather than longitudinal, and the

number of patients being affected by urinary symptoms in each age group is impossible to determine. Some patients may also have been represented more than once in the data set. We did not include samples sent from hospital clinics and wards because of the large number of specimens taken in specialist units (including intensive care, liver unit, urology and urogynecology), which may have skewed the results.

Ideally we would have liked to be able to determine whether each woman in the sample had reached menopause, so that we could compare pre- and postmenopausal women after controlling for age and other relevant factors (such as treatment with hormone replacement therapy) using logistic regression. This information was not available in the present study, so that we had to use the average age of the menopause (50 years [19]) as a proxy for the onset of estrogen deficiency. The present uptake of hormone replacement therapy in the UK and elsewhere in Europe is probably less than 15% of women aged 40–65 [20,21], with as many as 40% of women failing to complete 12 months of treatment even when there is a clear reason to do so [22]. The use of estrogen replacement in our study population is therefore unlikely to have had a significant effect on the results.

In conclusion, bacteriuria becomes more common in both men and women with increasing age. However, no specific changes appear to occur in the rate of infection or the infecting flora at the time of the menopause. It is therefore unlikely that pathophysiological changes in the urogenital tract which occur as a result of estrogen deficiency following the menopause have a significant impact on the prevalence of bacteriuria in community-dwelling women.

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EDITORIAL COMMENT: Urinary tract infections affect 20%–30% of women at some time and account for more than 5 million physician visits annually in the United States. Yet despite this high incidence and significant morbidity little is still known about why certain women are at risk and what can be done clinically to prevent UTIs. We know that women who are non-secretors of blood group antigens are three to four times more likely to have recurrent UTIs, probably because of increased adherence of *E. coli* to the uroepithelial cells. Other factors, such as the use of spermicides, a decrease in *Lactobacillus* colonization of the vagina, and presumably hypoestrogen status of the vagina, have been linked to recurrent bladder infections. This study provides an interesting insight into the natural risk of UTIs based on age alone. Because of the overwhelming number of patients, the increase in UTIs based solely on age must strongly be considered. Current studies, including the HERS trial, prospectively evaluating hormone replacement use should give more information on ERT and recurrent UTIs. I believe that these studies will concur with this analysis and find that ERT, especially oral preparations, have little effect on urinary tract infections.