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# Lower Urinary Tract Infections and the Effects of Hormone Therapy in Postmenopausal Women in the Zagreb Region

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## ABSTRACT

Urinary tract infections (UTI) remain one of the most common bacterial infections seen in adult women of all ages. In postmenopausal women, the aging process contributes to local complaints in the lower urogenital tissue, including UTI. Our study was conducted at gynecological practices of the health centers in the Zagreb region, Croatia, during 2009. The study included postmenopausal women with urinary symptoms divided into two groups: hormone therapy (HT) users and controls. The objectives were to estimate microbiologically proven lower UTIs (LUTIs) in postmenopausal women with urinary symptoms and the effect of regular HT use on microbiologically confirmed LUTIs. Out of 2338 postmenopausal patients, there was a significantly higher rate of women with urinary symptoms in HT users, namely 64.4% (143/221), compared to the control group at 4.8% (102/2116). Of the 245 patients with urinary symptoms, in 58.8% (144/245) the infection was microbiologically confirmed. Hormone therapy users showed a statistically significant lower rate of microbiologically proven LUTIs (46.9%, 67/143) compared to controls (75.5%, 77/102,  $p < 0.001$ ). Data analysis also showed the efficacy of local as well as systemic HT treatment compared with the control group ( $p < 0.00$ ,  $p = 0.049$ ). But there was a significant difference in the frequency of LUTIs between patients who used local (30.3%, 20/66) and systemic (61.1%, 47/77) HT ( $p < 0.001$ ). The patients who, regularly used therapy, in the local HT group as well as in the group on systemic HT, showed a lower incidence of LUTIs compared to controls ( $p < 0.00$ ,  $p = 0.006$ ). In patients who did not regularly use therapy, there were no significant differences between either local (63.6%, 7/11) or systemic (76.9%, 20/26) HT non-regular users and the control group (75.5%, 77/102) ( $p = 0.917$ ,  $p = 0.625$ ). The high percentage of patients with non-microbiologically confirmed LUTIs (41.2%, 101/245) suggested the significant role microbiological testing has in LUTI diagnosis. Both local and systemic HT use was related to LUTI reduction.

**Key words:** urinary tract infections, postmenopausal women, microbiological analysis, hormone therapy

## Introduction

Urinary tract infections remain one of the most common bacterial infections seen in adult women of all ages<sup>1,2</sup>. The prevalence of symptomatic UTIs or asymptomatic bacteriuria among women is believed to increase even further with age. Recent prospective studies found

that 10–15% of women over the age of 60 have frequent recurrences of UTI, with bacteriuria occurring in 10–15% of women aged 65–70 and 15–20% of women aged >80<sup>3,4</sup>. In Croatia, acute uncomplicated cystitis in women occurred more frequently in women over 40 years of

age, with altogether 65% of episodes of acute uncomplicated cystitis recorded in the age group 40–79 years<sup>5</sup>. According to epidemiological data, this amounts to a total of 825,094 women  $\geq 50$  years, constituting about one third of all the female population in Croatia<sup>6</sup>.

After menopause the vagina is more likely to be colonized with potential uropathogens and vaginal pH rises as the lactobacillus no longer predominates<sup>7</sup>. Physiological changes in the vaginal milieu contribute to UTI in postmenopausal women<sup>8</sup>. In order to avoid unnecessary antibiotic use in patients with UTI, microbiological testing is important.

When UTI is not confirmed by microbiological examination, the effective treatment option in postmenopausal women with urinary symptoms could be hormone therapy (HT).

Many studies indicate that estrogen (HT) use may reduce recurrent UTI and result in improvements in quality of life<sup>9–12</sup>. Regular use has important role in the positive effect of HT treatment on UTI. However, rates of use vary from 9 to 35% for women 40 to 60 years of age<sup>13,14</sup>.

There are very few available reports on the issue of postmenopausal health and HT use in Eastern Europe<sup>15</sup>. Sales figures in Croatia showed 523,351 prescribed cycles of postmenopausal hormonal replacement medication during 2001. Based on these data, one may estimate at 8.3% HT users in the target population of women aged 50 – 64<sup>15</sup>.

Therefore it was interesting to investigate UTI incidence in postmenopausal women in the Zagreb region, as well as the relation between UTI and regularity of HT use. Our investigation comprises lower UTIs (LUTIs): urethritis, cystitis and urethral syndrome.

In this study, the objectives were to estimate microbiologically proven LUTIs in postmenopausal women with urinary symptoms and investigate the effect of different type of HT regimen regularly used on microbiologically confirmed LUTIs.

## Material and Methods

### *Study population*

The study was carried out at gynecological practices of the health centers in the Zagreb region, Croatia, during 2009. Women aged 45–65 were included in the study. According to the data given in gynecological practices in study involved, there were 2338 women aged 45–65. Out of 2338 patients aged 45–65, there were 222 HRT users and 2116 non-HRT users. The study included 245 women who visited the gynecological practices because of urinary symptoms. Each patient had at least two urinary symptoms (dysuria, nocturnal frequency:  $\geq 2$ , diurnal frequency  $\geq 6$ , urgency). Exclusion criteria were any systemic disease or infection, suspected or proven malignant disease, unexplained uterine bleeding, previous hysterectomy or surgical correction in the urogenital tract.

The following specimens for microbiological analysis were obtained from each patient: urine samples for urine

culture and determination of the number of white blood cells (leukocytes) in urine sediment, cervicovaginal and urethral swab specimens. All specimens were obtained before antibiotic management.

Patients with microbiologically confirmed urethritis, cystitis or urethral syndrome, or mixed infection were considered to have LUTI.

In our study, regularity of HT use was defined in accordance with the answer to the question: »Do you or do you not forget to take medications once a month at least?«. All of the patients completed a questionnaire. The questionnaire covered socio-demographical information (age, level of education, present occupation, marital and socio-economic status), number of pregnancies, onset of menopause, time since last menses in years, urinary symptoms, duration of HRT in years, mode of HRT use (tablets, patches, cream, vaginal tablets/cream), regularity of HT use. All participants provided informed consent, and the study was approved by the Ethics Committee of the Croatian National Institute of Public Health.

### *Microbiological analysis*

Microbiological analysis of samples was performed at the Department of Microbiology and Bacteriology and the Molecular Diagnostics Department of the Croatian National Institute of Public Health. Significant bacteriuria and the presence of white blood cells in the urine sediment of symptomatic patients confirmed cystitis<sup>16</sup>. The presence of white blood cells in the urine sediment, a low number of microorganisms in the urine, and the presence of a single type of bacteria in high numbers in specimens of urethral swabs of symptomatic patients confirmed urethral syndrome<sup>17</sup>. The presence of a genital mycoplasmas or *C. trachomatis* in urethral swabs of symptomatic patients confirmed urethritis<sup>17</sup>.

All microorganisms cultured from the urine, urethral or cervicovaginal swabs were identified according to routine laboratory methods, including API-tests, Bio-Merieux. The diagnosis of urogenital mycoplasmas was confirmed by semiquantitative culturing tests Mycofast and MycoIST; Bio-Merieux and molecular detection was performed using real time PCR methodology on Applied Biosystems.

*C. trachomatis* identification was performed using PCR-Cobas Amplicor methodology by Roche.

### *Statistical analysis*

Statistical analysis was performed by SPSS ver. 17.01 (SPSS ID: 729038). The differences between groups, depending on the type of data, was assessed with parametric (t-test, ANOVA) or non-parametric (Fisher exact,  $\chi^2$ , Mann-Whitney U or Kruskal-Wallis) tests. The level of statistical significance was chosen to be 0.05.

## Results

Out of 2338 patients, 245 (10.4%) postmenopausal women with urinary symptoms who visited gynecological

practices during 2009 were included in the study population. One hundred and forty-three postmenopausal women on HT (HT group) and 102 postmenopausal women with no therapy (control group) completed the study. The majority of women on HT (77/143, 53.8%) were systemic (continuously combined or sequential) therapy users and 66 women (66/143, 46.1%) were local HT users.

The mean age of the HT patients (N=143) was 57.08±4.89 years, while that of the control patients (N=102) was 56.13±5.091 years. There was no statistically significant difference between the two study groups regarding age (p=0.125), onset of menopause (p=0.418), and years in menopause (p=0.434). The mean number of previous childbirths per patient was also similar in both groups: 1.68±0.728 for HT patients and 1.58±0.838 for control patients (p=0.192). Marital status, level of education and nicotinism were proportionally similar in both groups (Table 1).

In the postmenopausal control group there were 102/2116 (4.8%) women with urinary symptoms, compared to 143/222 (64.4%) in the HT-user group (p<0.001, Table 2). Of the 245 patients with urinary symptoms, an infectious etiology was found for 144/245 (58.8%) patients. The most frequent microbiologically proven LUTI agents were *Escherichia coli* (110/144, 76.3%) and *Ureaplasma urealyticum* (101/144, 79.1%).

In the HT patients there was a statistically significant lower rate of microbiologically proven LUTIs (67/143, 46.9%) compared to controls (77/102, 75.5%) (p<0.001, Table 2).

Furthermore, a comparison between the local HT and systemic HT users showed a significantly decreased number of patients with LUTIs in the local HT group (30.3%, 20/66 vs. 61.1%, 47/77, p<0.001, Table 3).

**TABLE 1**  
CHARACTERISTICS OF STUDY PATIENTS

Characteristics	HRT – group (N=143) X±SD*	Control group (N=102) X±SD	p
Age (years)	57.14±4.898	56.13±5.091	0.125
Menopause (age)	49.97±5.050	49.67±2.611	0.418
Years in menopause	7.10±4.667	6.45±4.041	0.434
No. of children			0.192
Marital status			0.055
Single	1 (0.7)	0 (0)	
Married	120 (83.9)	92 (90.2)	
Widowed	19 (13.3)	5 (4.9)	
Divorced	3 (2.1)	5 (4.9)	
Level of education			0.052
Low (Primary school)	102 (71.3)	61 (59.8)	
Intermediate (Secondary school)	36 (25.2)	35 (34.3)	
High (University)	5 (3.5)	6 (5.18)	
Nicotinism			1.000
Yes	12 (8.4)	8 (7.8)	
No	131 (91.6)	94 (92.2)	

Note: Data are no.(%) of subjects or  $\bar{X}\pm SD$ . \* SD=standard deviations

**TABLE 2**  
COMPARISON OF PATIENTS WITH SYMPTOMS AND MICROBIOLOGICALLY PROVEN LUTIs\* IN HT USERS AND NON-USERS

Groups of patients	HT users n/N (%)	HT non-users n/N (%)	Total n/N (%)	p <sup>a</sup>
Urinary symptoms	143/222 (64.4)	102/2116 (4.8)	245/2338 (10.4)	<0.001
Microbiologically* proven LUTIs	67/143 (46.9)	77/102 (75.5)	144/245 (58.4)	<0.001

\* Patients with microbiologically proven infections affecting lower urinary tract (cystitis, urethritis, urethral syndrome or mixed infection) among patients with urinary symptoms, n - number of patients with urinary symptoms or LUTIs, N - number of patients in group

<sup>a</sup> Comparison of HT users and HT non-users

**TABLE 3**  
MICROBIOLOGICALLY PROVEN LUTIs\* REGARDING TYPE AND REGIMEN OF HT

Groups of patients	Systemic HT n/N (%)	Local HT n/N (%)	Total HT n/N (%)	Controls n/N (%)	p <sup>a</sup>	p <sup>b</sup>	p <sup>c</sup>	p <sup>d</sup>
Total sample	47/77 (61.0)	20/66 (30.3)	67/143 (46.9)	77/102 (75.5)	<0.001	0.049	<0.001	<0.001

<sup>a</sup> Comparison of systemic and local HT group; <sup>b</sup> Comparison of systemic HT group and control group; <sup>c</sup> Comparison of local HT group and control group; <sup>d</sup> Comparison of both HT groups and control group

\* Patients with microbiologically proven infections affecting lower urinary tract (cystitis, urethritis, urethral syndrome or mixed infection), n - number of patients with LUTIs, N - number of patients in group

**TABLE 4**  
MICROBIOLOGICALLY PROVEN LUTIs\* REGARDING REGULARITY OF HT USE

Groups of patients	Systemic HT n/N (%)	Local HT n/N (%)	Total HT n/N (%)	Controls n/N (%)	p <sup>a</sup>	p <sup>b</sup>	p <sup>c</sup>	p <sup>d</sup>
HT regulary used	27/51 (52.5)	13/55 (23.6)	40/106 (37.7)	77/102 (75.5)	0.003	0.006	<0.001	<0.001
HT non-regulary used	20/26 (76.9)	7/11 (63.6)	27/37 (72.9)	77/102 (75.5)	0.670	0.917	0.623	0.763

<sup>a</sup> Comparison of systemic and local HT group; <sup>b</sup> Comparison of systemic HT group and control group; <sup>c</sup> Comparison of local HT group and control group; <sup>d</sup> Comparison of both HT groups and control group

\* Patients with microbiologically proven infections affecting lower urinary tract (cystitis, urethritis, urethral syndrome or mixed infection), n - number of patients with LUTIs, N - number of patients in group

Data analysis also showed the efficacy of local as well as systemic HT treatment compared with the control group ( $p < 0.001$  and  $p = 0.049$ , Table 3).

There were 106/143 (74.12%) women who use HT regulary or regulary HT users as compared with 37/143 (25.87%) non-regulary HT users. There was no statistical difference between the systemic and local HRT groups in relation to regulary of HT use (48.1%, 51/106 vs. 51.9%, 55/106,  $p = 0.22$ , Table 4.).

Patients in the local HRT group, as well as the systemic HRT patients who regulary used HT, showed a lower incidence of LUTIs compared to controls ( $p < 0.001$  and  $p = 0.006$ , Table 4).

There was a statistically significant decrease in the incidence of LUTIs in patients who regulary used local HT in comparison to those who regulary used systemic HT ( $p = 0.003$ ).

In non-regulary HT patients, there was no statistical difference between local and systemic HT users regarding LUTIs (63.6%, 7/11 vs. 76.9%, 20/26,  $p = 0.670$ ). Also, there were no significant differences between either local or systemic HT non regular users and the control group (63.6%, 7/11 vs. 75.5%, 77/102,  $p = 0.917$ ; 76.9%, 20/26 vs. 75.5%, 77/102,  $p = 0.625$ , Table 4).

## Discussion

The aging process in postmenopausal women contributes to local problems in the lower urogenital tissue, including UTI, which adversely affect the quality of the

women’s lives<sup>18</sup>. In older postmenopausal women, the clinical presentation of UTI is somewhat different than in younger women. Postmenopausal women are less likely to report frequency, dysuria, hematuria or fever, but are more likely to report flank pain<sup>19</sup>. Also, in postmenopausal women, there are a variety of urogenital complaints and symptoms due to atrophy of the urogenital mucosa.

In our study, out of 2338 patients between 45 and 65 years of age, 10.4% (245/2338) had urinary symptoms: in the control group there were only 4.8% (102/2116) women with urinary symptoms, compared to as many as 64.4% (143/221) in HT users. The possible explanation for the significantly higher incidence of urinary symptoms in HT users is that women who expressed urinary symptoms visit the doctor more in order to get the HT. Also, it is possible that HT users are better informed and generally more concerned about their health.

Despite the fact that an accurate diagnosis of UTI depends on both the presence of symptoms and a positive urine culture, in most outpatient settings this diagnosis is made without the benefit of the culture.

Thus, one of the objectives of this study was to estimate the incidence of microbiologically proven LUTI in postmenopausal women with urinary symptoms.

The results showed that only about half of the postmenopausal women with urinary symptoms had microbiologically proven LUTIs (58.8%, 144/245). In HT patients there were fewer microbiologically proven LUTIs compared to controls (46.9%, 67/143, vs. 75.5%, 77/102). It is possible that the HT patients were not objective in

answering the question about urinary symptoms. Also, it is possible that some of them had urogenital complaints associated with symptoms of vaginal atrophy or urogenital aging at the same time. The problem in postmenopausal women is to differentiate urinary symptoms from those of urogenital aging.

The LUTI incidence in our patients was higher (58.8%, 144/245) compared to Hextall et al.<sup>20</sup>, who reported the prevalence of UTIs related to estrogen deficit to range between 20–30% in the references.

According to our results, in a high percentage of women (41.2%, 101/245) no infection was microbiologically proven, despite the urinary symptoms. Also, there was no significant difference between women with microbiologically confirmed infection and those with non-confirmed infection (58.8%, 144/245 vs. 41.2%, 101/245). A microbiological analysis is, therefore, necessary for appropriate treatment and avoidance of unnecessary antibiotic use.

The second objective was to estimate the impact of regularity of HT use (including systemic and local modes) on LUTI. According to many investigations<sup>21</sup>, one of the benefits of HT is the restoration of lactobacilli vaginal flora associated with a protective effect against urogenital infections.

In our study, a significantly lower percentage of LUTIs was detected in HT users when compared to the control group (46.9%, 67/143 vs. 75.5%, 77/102,  $p < 0.001$ ). This result stressed the positive effect of HT treatment on LUTIs.

Although systemic HRT is frequently used, the role of oral hormone therapy in reducing urinary infections remains unclear<sup>22–24</sup>. Many investigators showed that only local HRT decreased the incidence of LUTIs<sup>25,26</sup>: randomized trials have shown that vaginal estrogen therapy prevents UTI in postmenopausal women with recurring UTI<sup>7,27</sup>. The amount of oral hormone that reaches the vaginal mucosa may be too low to affect the colonization of uropathogens<sup>28</sup>. Our study is in accordance with previously mentioned investigations. Comparing local and systemic HT use, the result showed that the incidence of LUTIs was significantly reduced in local HT users as compared to systemic users (30.3%, 20/66 vs. 61.0%, 47/77,  $p < 0.001$ ), or even compared to controls (30.3%, 20/66 vs. 75.5%, 77/102,  $p < 0.001$ ). Although the comparison between systemic HT users and controls also showed a statistically significant difference (61.0%, 47/77,

vs. 75.5%, 77/102,  $p = 0.049$ ), it seems that local HT use was more frequently associated with LUTI reduction.

Hormone replacement medication must be regularly used and administered strongly according to doctors' prescriptions. In the study of Fistonja et al.<sup>14</sup>, the authors informed about poor persistence with long-term HT in Croatia. According to our investigation, the majority of patients were regular HT users (74.12%, 106/143). There was no statistical difference between the local and systemic HT groups regarding regularity of HT use (51.9%, 55/106 vs. 48.1%, 51/106  $p = 0.22$ ).

In our study, regular use resulted in LUTI reduction, both in local and systemic HT users. Moreover, regular local HT users had a significantly lower percentage of LUTIs than systemic regular HT users ( $p = 0.003$ ). However, in non-regular users, there was no statistical difference between local and systemic HT users with regard to LUTIs ( $p = 0.670$ ).

The possible reason for high number of regular HT users is that the study involved women in the metropolitan area of Zagreb, where patients are better informed about the advantages of HT, have a higher socio-economic status and better access to gynecological practices. However, it is possible that the main limitation of our study is the generalizability of data, due to the scope of the metropolitan area population tested.

In conclusion, LUTIs were microbiologically proven in 58.8% (144/245) of postmenopausal women with urinary symptoms. The high percentage of patients with non-microbiologically confirmed LUTIs (41.2%, 101/245) suggested the significant role microbiological testing has in LUTI diagnosis. Therefore, microbiological analysis is necessary for appropriate treatment and avoidance of unnecessary antibiotic use. The incidence of LUTIs was significantly lower in both groups of HRT users (local and systemic), and confirmed that HRT use was associated with LUTI reduction in the population of postmenopausal women in the Zagreb region.

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## INFEKCIJE DONJEG DIJELA MOKRAĆNOG SUSTAVA I UTJECAJ HORMONSKOG LIJEČENJA U ŽENA U POSTMENOPAUI NA PODRUČJU ZAGREBA

### SAŽETAK

Infekcije mokraćenog sustava (IMS) spadaju među najčešće infekcije žena svih dobi. Kod žena u postmenopauzi, proces starenja doprinosi lokalnim promjenama tkiva donjeg dijela urinarnog sustava, uključujući pojavu IMS. Tijekom 2009. provedena je prospektivna studija u ginekološkim ordinacijama Domova zdravlja na području Zagreba, na skupini žena u postmenopauzi s urinarnim simptomima. Ispitanice su podijeljene u dvije skupine: žene koje uzimaju hormonsko liječenje (HL) i kontrolnu skupinu. Ciljevi ovog rada bili su ustanoviti postotak mikrobiološki dokazanih infekcija donjeg dijela mokraćenog sustava (DIMS) u postmenopausalnih žena s urinarnim simptomima i utjecaj HL na mikrobiološki potvrđene DIMS kod žena koje redovito/neredovito uzimaju HL. Od ukupno 2338 žena, statistički značajno više žena s urinarnim simptomima bilo je u skupini na HL (64,4%, 143/221) nego u kontrolnoj skupini (4,8%, 102/2116,  $p < 0,001$ ). Međutim, od 245 ispitanica s urinarnim simptomima, DIMS je mikrobiološki potvrđena samo u 58,8% (144/245) od njih. U skupini žena na HL bilo je statistički značajno manje pacijentica sa mikrobiološki dokazanom DIMS (46,9%, 67/143) u usporedbi s kontrolama (75,5%, 77/102,  $p < 0,001$ ). Utvrđena je učinkovitost lokalnog ali i sistemskog HL u sprječavanju DIMS u usporedbi s kontrolnom skupinom ( $p < 0,001$ ,  $p = 0,049$ ). Međutim, u skupini na HL, između ispitanica na lokalnom (30,3%, 20/66) i sistemskom liječenju (61,1%, 47/77) ustanovljena je statistički značajna razlika u učestalosti DIMS ( $p < 0,01$ ). U skupini ispitanica koje redovno uzimaju HL, lokalno ili sistemski, također je ustanovljeno statistički značajno manje DIMS nego u kontrolnoj skupini ( $p < 0,0$ ,  $p = 0,06$ ). U skupini koja neredovno uzima HNL nije nađena razlika u učestalosti DIMS između žena na lokalnom (63,%, 7/11) ili sistemskom (76,9%, 20/26) HL te kontrolne skupine (75,5%, 77/102,  $p = 0,917$ ,  $p = 0,625$ ). Obzirom da kod velikog broja ispitanica (41,2%, 101/245), DIMS nije potvrđena mikrobiološkom pretragom, zaključujemo da je primjena mikrobiološke dijagnostike neophodna za postavljanje točne dijagnoze DIMS. Na smanjenu učestalost DIMS utjecala je primjena lokalnog ali i sistemskog HL.