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Postmenopausal hormone therapy and incident urinary incontinence in middle-aged women

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Abstract

Objective—To examine the association of hormone therapy with incident urinary incontinence (UI) in postmenopausal women aged 37–54 years in the Nurses' Health Study II.

Study Design—Participants reported use of hormone therapy, including hormone type, on biennial questionnaires from 1989 to 2001. Among 7,341 postmenopausal women reporting no UI in 2001, we identified 1,026 women who developed UI at least monthly between 2001 and 2003. Multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

Results—Women currently using hormone therapy had 1.39-fold (95% CI 1.16–1.67) increased odds of incident UI compared with women who never used hormone therapy. Odds ratios were similar in current users of oral estrogen alone (OR 1.35, 95% CI 1.03–1.78) and oral estrogen with progestin (OR 1.37, 95% CI 1.13–1.67).

Conclusion—These findings suggest an increased risk of UI associated with use of postmenopausal hormone therapy in younger postmenopausal women.

Keywords

epidemiology; hormone replacement therapy; menopause; urinary incontinence

INTRODUCTION

Estrogen receptors have been identified throughout the pelvic floor, including the urethra, vaginal wall, bladder trigone, and uterosacral ligaments, and loss of estrogen after menopause has been associated with urogenital atrophy and increases in urinary symptoms.¹ Yet, recent data from large-scale prospective studies, including randomized trials, have demonstrated increased risks of incident urinary incontinence (UI) and worsening UI severity among women using hormone therapy.^{2–5} A positive association between hormone therapy and the risk of stress UI may be explained by estrogen's role in decreasing the collagen concentration of the connective tissues supporting the urethra^{6, 7} while increasing bladder contractility.^{8, 9} In

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addition, it is possible that adverse neurovascular effects of hormone therapy^{10, 11} result in damage to bladder innervation and lead to urge UI. However, it is unclear from limited existing data whether HT similarly affects stress and urge UI.

The majority of studies of hormone therapy and UI, particularly the large randomized trials^{3, 4}, have only been able to address women aged 60 years and older, and data on hormone use and UI in younger postmenopausal women are lacking. The importance of certain UI risk factors may differ between older and younger women,¹² especially since we have observed a decreasing incidence of stress UI and a large increase in incidence of urge UI with increasing age.¹³ Therefore, if hormone therapy is associated with risk of a particular incontinence type, its importance as a UI risk factor might vary between older and younger post-menopausal women.

Here, we prospectively examined the association between postmenopausal hormone use, including hormone type, with incident urinary incontinence in postmenopausal women aged 37–54 years enrolled in an observational cohort study. Although such observational studies can have confounding, observational studies and randomized clinical trials of hormone use and UI in older women have found nearly identical associations, indicating the observational study design is a valid tool to assess this association.

MATERIALS AND METHODS

Study population

The Nurses' Health Study (NHS) II, modeled after the original Nurses' Health Study¹⁴, was established when 116,671 female nurses aged 25 to 42 years responded to a mailed questionnaire in 1989. Information about participants has been updated using biennial questionnaires. To maximize participation during each questionnaire cycle, the full-length questionnaire is sent for initial mailings, after which an abbreviated version of the questionnaire is sent to non-responders. To date, the follow-up rate in NHS II is approximately 90%. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Questions about UI frequency and quantity were included on the full-length questionnaires mailed in 2001 and 2003. The full-length versions of both questionnaires were completed by 70,712 women. These women were similar to the entire cohort in mean age (47 years in both), mean body mass index (BMI; 27 kg/m² in both), parity (81% vs. 82% parous, respectively), and current use of postmenopausal hormone therapy (13% vs. 15% in both). These analyses were restricted to women who had reported natural menopause, hysterectomy with bilateral oophorectomy, or menopause due to radiation or chemotherapy as of the 2001 questionnaire (n=17,193).

We excluded women missing data on hormone therapy use (n=27), UI frequency (n=95), and key UI risk factors, including parity (n=114) and body mass index (n=87). This analysis focused on incident incontinence between 2001 and 2003, thus, women who reported UI at least once per month (n=7,794) or UI less than once per month of quantities at least enough to wet the underwear (n=1,385) in 2001 were also excluded at baseline. Because a change in health status may influence use of hormone therapy and affect UI risk, and thus cause confounding, we excluded women with major health conditions at baseline, including stroke, multiple sclerosis, and Parkinson's disease (n=138), as well as women with functional limitations (n=212). Thus, 7,341 postmenopausal NHS II participants were at-risk for incident UI in 2001, and included in these analyses.

Measurement of urinary incontinence

In 2001 and 2003, participants were asked, “During the last 12 months, how often have you leaked or lost control of your urine?” Response options were: never, less than once per month, once per month, 2 to 3 times per month, about once per week, and almost every day. Participants reporting incontinence were then asked, “When you lose your urine, how much usually leaks?” Response options were: a few drops, enough to wet your underwear, enough to wet your outer clothing, and enough to wet the floor. High reproducibility of responses to these questions was demonstrated in a similar group of nurses.¹⁵

We defined incident incontinence as leakage occurring at least once per month in 2003. A supplementary questionnaire that included validated questions to assess UI type¹⁶ was mailed to women who reported incident UI occurring at least weekly (n=287) because we believed that these women were likely better able to describe the precipitants of their incontinence than women with less frequent symptoms. We assessed UI type among women who returned the supplementary questionnaire and responded to all of the UI type questions (n=221). We defined stress UI as leakage occurring mostly with active increases in abdominal pressure, such as with coughing or sneezing, lifting things, laughing, or exercise. Incontinence occurring mostly with symptoms of urgency, such as when a toilet was inaccessible or with a sudden feeling of bladder fullness, was considered urge UI. For all analyses, non-cases were those women who reported no UI or UI of a few drops less than once per month again in 2003.

Measurement of postmenopausal hormone use

In 1989, participants were asked whether they had ever used postmenopausal hormone therapy and, if so, the type of hormone used most recently. Questions about use of postmenopausal hormone therapy during the previous 2 years as well as the hormone type have been included on each subsequent biennial questionnaire. This information was used to categorize participants as never, past, or current users of postmenopausal hormone therapy and, among current users, the type of hormone in 2001. In addition, among current users of oral conjugated estrogen, self-reported information on estrogen dose was used to classify women as lower- (<1.25 mg) or higher- (≥1.25 mg) dose users.

Statistical analysis

In our study population of postmenopausal women, we had limited power to examine weekly UI or more severe UI. Thus, our primary analyses focused on incident incontinence at least monthly. Relations with incontinence type, which was classified only among incident cases with at least weekly UI, were examined in secondary analyses. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated using multivariable logistic regression models. Each analysis included only women meeting the case definition of interest and the non-cases (eg, in analyses of urge UI, we excluded cases of stress UI). All analyses were adjusted for potential confounding factors, including age (≤40, 41–45, 46–50, > 50 years), parity (0, 1–2, ≥3 births), body mass index (continuous), race/ethnicity (white, black, Hispanic, Asian, other/missing), cigarette smoking (never, past, current), hysterectomy, and previous use of oral contraceptives. Additional adjustment for type 2 diabetes and use of diuretics did not change results and, thus were not included in the final models. All covariate information was self-reported as of the 2001 questionnaire.

RESULTS

In 2001, study participants were age 37 to 54 years. Compared with women who never used postmenopausal hormone therapy, past and current hormone therapy users were less likely to be current cigarette smokers and more likely to have undergone bilateral oophorectomy (Table 1).

Over 2 years of follow-up, 14% of the participants developed incontinence at least monthly and 4% developed incontinence at least weekly. Among those cases with at least weekly UI and data on UI type, 55% were classified as stress incontinence and 18% were classified as urge incontinence, while the remainder had mixed or other UI types.

After control for confounding, the odds of incident UI in current users of postmenopausal hormone therapy were 1.39 (95% CI 1.16–1.67) times that in women who never used postmenopausal hormone therapy (Table 2). There was no significant elevation in the odds of incident UI in past hormone users compared with never users. Results were similar when we restricted the analyses to women who reported natural menopause ($n=4,482$) (data not shown in table). For example, among women with natural menopause, the multivariable-adjusted odds ratios were 1.41 (95% CI 1.15–1.72) for current users of hormone therapy and 1.14 (95% CI 0.87–1.50) for past users. In analyses of incontinence type, although we had limited power, there was no clear indication that relations with current hormone use were statistically different for stress (OR 1.09, 95% CI 0.68–1.74) versus urge UI (OR 1.72, 95% CI 0.74–3.97).

Current use of oral estrogen alone and oral estrogen plus progestin were similarly associated with significant 35–37% increases in the odds of incident at least monthly UI (Table 3). The odds ratio for incident UI among current users of transdermal estrogen alone or with progestin was comparable to that of the other hormone types (OR 1.41, 95% CI 0.98–2.01). However, only a small proportion of women reported using transdermal hormonal therapy and the association was borderline statistically significant.

In analyses of oral conjugated estrogen dose, higher estrogen doses did not appear to be associated with greater UI odds than lower doses (data not shown in table). For example, odds ratios for any UI were 1.16 (95% CI 0.90–1.49) among women currently taking doses less than 1.25 mg and 1.31 (95% CI 0.91–1.88) for women currently taking doses of 1.25 mg or higher compared with women who never used hormone therapy. However, power for this analysis was somewhat limited.

COMMENT

Among these women aged 37 to 54 years, current use of postmenopausal hormone therapy was associated with moderately increased odds of developing UI. This increase in odds did not appear to vary by hormone type or route of administration.

Previous observational studies^{2, 17, 18} and randomized controlled trials^{3, 4} in older women have found an increased risk of UI among current users of postmenopausal hormone therapy, including both estrogen alone and combined with progestin. In general, these risks have been consistent in magnitude with those we report here for younger postmenopausal women, indicating that HT has similar associations with overall UI regardless of the age at which it is taken. For example, women assigned to oral estrogen alone and those assigned to oral estrogen plus progestin had 40–50% increased risks of incident UI in a randomized controlled trial of over 23,000 postmenopausal women aged 50 to 79 years (RRs 1.53, 95% CI 1.37–1.71 and 1.39, 95% CI 1.27–1.52, respectively).³ Likewise, among over 39,000 postmenopausal women aged 50–75 years in the Nurses' Health Study I, relative risks for UI were increased by about 50% and varied little across hormone types, ranging from 1.45 (95% CI 1.33–1.57) among current users of oral estrogen alone to 1.60 (95% CI 1.27–2.02) among current users of transdermal estrogen and progestin.²

The exact role of hormone therapy in UI risk is not well understood, although the similarities in the relation of UI with HT across age groups suggest that multiple mechanisms may be acting. Indeed, several possible mechanisms have been proposed. For example, observed decreases in paraurethral collagen concentration and cross-linking^{6, 7}, increases in mRNA

levels for collagen types I and III⁶, and increased matrix metalloproteinase-2 activity⁷ in women taking estrogen therapy indicate increased collagen turnover, and suggest that estrogen supplementation may weaken the structure of the connective tissues supporting the urethra. In addition, animal studies have found increases in the smooth muscle to collagen ratio, vascular density, and contractility of the bladder with estrogen supplementation.^{8, 9} Taken together, these changes may increase the risk of stress UI. Furthermore, hormone therapy is associated with neurovascular disease^{10, 11}, which could possibly affect bladder innervation and risk of urge UI.

Several limitations of this study should be noted. First, all information on UI was self-reported. However, self-reports of UI were highly reliable in a similar population of nurses.¹⁵ In addition, among 456 women, Diokno et al¹⁹ reported 83% agreement between self-reported incontinence and clinical diagnosis.

Information on use of postmenopausal hormone therapy was also self-reported. However, we believe that reports of medication use are accurate in this cohort of health professionals. To minimize potential confounding, we restricted the study population to women without major health conditions and adjusted for multiple potential confounding variables. However, we cannot rule out residual confounding in an observational study. Finally, only a small proportion of the participants in the NHS II cohort are non-white. Thus, it is possible that our findings are not generalizable to minority populations, in addition to women with major health conditions.

In conclusion, our finding of an increase in UI among middle-aged women currently using postmenopausal hormone therapy is comparable to findings from previous large-scale studies, including randomized clinical trials, in older women. Together, these results suggest that urinary incontinence should be considered as a modest risk of hormone therapy use for postmenopausal women across age groups. Further research is necessary to better understand the mechanisms linking hormone therapy with urinary incontinence development.

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Table 1

Characteristics of study participants at risk for incident urinary incontinence according to postmenopausal hormone use in 2001

Characteristics	Postmenopausal Hormone Use		
	Never (n=1,868)	Past (n=1,033)	Current (n=4,440)
Mean age (SD), years	50.8 (3.3)	50.9 (3.4)	50.2 (3.6)
Mean body mass index (SD), kg/m ²	26.5 (6.0)	26.3 (5.4)	26.0 (5.4)
Type of menopause (%)			
Natural	84.8	69.4	49.9
Bilateral oophorectomy	4.4	27.8	49.1
Radiation or chemotherapy	10.8	2.8	1.0
Hysterectomy (%)	6.1	29.0	51.5
Race (%)			
White	92.4	93.0	93.4
Black	1.7	1.8	1.0
Hispanic	1.2	1.1	1.2
Asian-American	2.1	1.3	1.3
Other/missing	2.6	2.8	3.1
Parity (%)			
0 livebirths	24.2	22.5	25.2
1–2 livebirths	51.0	55.3	54.5
≥3 livebirths	24.8	22.2	20.3
Cigarette smoking (%)			
Past	26.5	31.1	28.8
Current	13.4	11.0	10.8
Ever used oral contraceptives (%)	80.6	87.1	90.3

Table 2Postmenopausal hormone use and odds of incident incontinence^a from 2001 to 2003

Postmenopausal hormone use	Non-cases	Cases	Age-adjusted OR (95% CI)	Multivariable- adjusted ^b OR (95% CI)
Never	1,568	211	1.00	1.00
Past	844	140	1.23 (0.98–1.55)	1.20 (0.96–1.53)
Current	3,546	675	1.41 (1.20–1.67)	1.39 (1.16–1.67)

^a Incontinence defined as leaking urine at least once per month^b Adjusted for age, parity, body mass index, race/ethnicity, cigarette smoking, hysterectomy, oral contraceptive use

Table 3Current postmenopausal hormone use and odds of incident incontinence^a from 2001 to 2003

Postmenopausal hormone use	Non-cases	Cases	Age-adjusted OR (95% CI)	Multivariable- adjusted ^b OR (95% CI)
Never	1,568	211	1.00	1.00
Current, type of hormone				
Oral estrogen alone	1,417	287	1.51 (1.24–1.83)	1.35 (1.03–1.78)
Oral estrogen and progestin	1,538	268	1.29 (1.06–1.57)	1.37 (1.13–1.67)
Transdermal estrogen alone or with progestin	295	61	1.53 (1.12–2.09)	1.41 (0.98–2.01)

^a Incontinence defined as leaking urine at least once per month^b Adjusted for age, parity, body mass index, race/ethnicity, cigarette smoking, hysterectomy, oral contraceptive use