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ORIGINAL ARTICLE

Increased risk for stress urinary incontinence in women with postmenopausal hormone therapy

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Abstract

Introduction and hypothesis The impact of estradiol-based hormone therapy (HT) on the incidence of stress urinary incontinence (SUI) is unknown. Therefore, we compared the use of such HT regimens and tibolone in women with and without SUI.

Methods The women with a history of SUI operation ($N = 15{,}002$) were identified from the Finnish National Hospital Discharge Register, and the control women without such an operation ($N = 44{,}389$) from the Finnish Central Population Register. The use of HT was traced from the National Drug Reimbursement Register, and the odd ratios (ORs) with 95% confidence intervals (95% CIs) for SUI were calculated by using the conditional logistic regression analysis.

Results The cases had used any HT more often than the controls. The use of systemic estradiol-only or estradiol–progestin therapy was accompanied by an increased SUI risk (OR 3.8, 95% CI: 3.6–4.0 and OR 2.7, 95% CI: 2.6–2.9 respectively). The use of estradiol with noretisterone acetate showed a higher risk of increase than that with medroxyprogesterone acetate. Age over 55 years at the initiation of systemic HT was accompanied by a higher SUI risk increase than that under 55 years of age. The use of tibolone, an estradiol + levonorgestrel-releasing intrauterine device, or vaginal estradiol also increased the risk.

Conclusions The use of HT regimens may predispose to the de novo development or worsening of pre-existing SUI. Thus, caution is needed when these regimens are prescribed to women with mild stress-related urine leakage or with established SUI risk factors.

Keywords Estradiol · Hormone therapy · Menopause · Stress urinary incontinence

Introduction

Stress urinary incontinence (SUI) is the most common form of incontinence [1]. The etiology of SUI is not understood in detail, but evidently a failure of pelvic support is of primary importance in its genesis. This claim is supported by the data that SUI is often preceded by conditions with high intra-abdominal pressure, such as pregnancy, with or without vaginal delivery, obesity, and strenuous physical work [1]. However, SUI can occur even in nulliparous women and without any preceding risk factors, implying an inherent SUI tendency [2].

Receptors for estrogen and progesterone are present in the urogenital tract and pelvic floor [3, 4]. This may imply that these hormones are of importance for continence. Indeed, estrogen increases urethral closure pressure, perhaps partly through improved blood flow [5]. It has also been shown that in postmenopausal women, estrogen strengthens the epithelia in the vagina and in the urethra and bladder wall [6]. Therefore, the use of postmenopausal hormone therapy (HT) should be expected to decrease the risk of SUI. However, a Cochrane analysis concluded that the use of systemic HT is accompanied by increases in the risk of overall urinary incontinence, whereas vaginal use of estrogens may decrease this risk [7]. In these studies, conjugated equine estrogen (CEE), alone or combined with medroxyprogesterone acetate (MPA),

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have been predominantly used. Indeed, 1-year therapy with CEE alone or CEE + MPA predisposed to both stress and urge incontinence in women who were continent before the start of HT [8]. Because CEE is a mixture of various estrogenic and anti-estrogenic compounds [9], the CEE-based data may not be directly applicable to HT containing natural estradiol, and therefore, the possible impact of estradiol on SUI risk may be different from that of CEE. However, the data on the effect of estradiol-based regimens on SUI risk are scanty. Furthermore, progestins may affect the SUI risk, either through a direct tissue effect or by modifying the effect of estrogen, but so far data on SUI risk exist only for MPA in combination with CEE [9].

In a large majority of clinical studies, the diagnosis of SUI has been based on patient questionnaires [7, 8, 10–12]. However, such a subjective diagnosis may be inaccurate and thus a possible source of error regarding the effect of HT on the risk of SUI may exist. The diagnosis of SUI can be expected to be most accurate in women who have been operated for SUI. Therefore, to study the possible effect of various HT on the risk of SUI, we compared the use of HT regimens in women with and without SUI operation.

Subjects and methods

Cases

We studied women with SUI ($N = 15{,}002$) who had undergone a tension-free tape operation, via either the retropubic or the transobturator route [13, 14] between 1994 and 2011 in 18 surgery units covering the whole of Finland. The diagnosis of SUI was based, in addition to a patient's careful report of the symptoms, on the gynecologist's objective evaluation of urinary leakage during coughing or jumping, or by urodynamic tests. The cases were collected from the Nationwide Hospital Discharge Register, which is under the control of the medical authorities.

Controls

For each case, 3 controls without a history of SUI operation in the discharge register ($N = 45{,}006$) were collected from the Finnish National Population Register. The controls were matched in regard to age (± 1 month), number of deliveries, and hospital district. A total of 617 controls were excluded because they failed to meet all the inclusion criteria, and thus, the final control group consisted of 44,389 women.

The use of postmenopausal hormone therapy

The use of HT by the cases and controls was assessed up to the time of operation from the National Drug Reimbursement Register. In Finland, HT regimens that are available only with a physician's prescription are only partially reimbursed (40–60% of the price). At each pharmacy visit, HT can be purchased for 3 months. The National Drug Reimbursement Register was initiated in 1994, and thus a woman buying HT regimens during the opening year, 1994, was considered to have started the use of systemic HT at the age of 52 years, and the use of vaginal estradiol at the age of 65, the mean ages of starting HT in this population [15], and the duration of preregister HT use was approximated accordingly. From 1995 onward to the end of 2011, the use of all HT regimens could be accurately traced from the register.

Estradiol is the basis for systemic HT regimens in Finland. According to the national guidelines, only hysterectomized women are allowed to use systemic estradiol-only (ET) regimen. Estradiol is given either orally (90%) or transdermally as a gel or a patch (10%). Oral estradiol doses are usually 1–2 mg/day and those of transdermal estradiol 25–100 μg/ day. Because of the similar estrogenic activity obtained by oral and transdermal ET use, we analyzed women using ET orally or transdermally as a single group (8,502 women in the whole series, 14.3%). In contrast, nonhysterectomized women used estradiol in combination with various progestins (EPT; $n = 17{,}371$, 29.2%; Table 1). Of the various progestins, norethisterone acetate (NETA) and MPA are the most common [16], but NETA-EPT alone or MPA-EPT alone had been used by 3,746 (6.3%) and 2,621 (4.4%) women respectively (Table 1). Those women who had switched from one EPT regiment to another, or who had been exposed to NETA, MPA, dydrogesterone, mesterolone or lynestrenol were categorized to other/mixed-EPT ($n = 10{,}304$, 17.3%). Levonorgestrel-releasing intrauterine device-EPT (Levo-IUD-EPT) was used by 423 (0.7%) women and tibolone by 277 (0.5%) women. A possible concomitant use of local vaginal estradiol in addition to systemic HT was not taken into account. In contrast, a total of 2,675 (4.5%) women had used only local estradiol intravaginally (Vagifem®; Novo Nordisk, Copenhagen, Denmark, 25 μg twice a week), and these women were analyzed as a separate group (Table 1).

Statistical analyses

The exposure time to various HT regimens was calculated from the purchase of the first regimen in women starting the use in 1995 or later, or from the age of 52 years in women using systemic HT and from the age of 65 for women who were using these regimens at the register opening. The HT exposure was considered to have ended at the purchase of the last HT regimen plus 3 months, or at the date of the SUI operation. The follow-up time refers to the time elapsed since the initiation of HT use to the time of SUI operation. The categorical variables were compared using the Chi-squared test. The association between HT exposure and risk of SUI

Table 1 The rate (*n*, %) of use of various hormone regimens, and times of hormone exposures (years, mean ± SD) and follow-up (years, mean ± SD) in the cases and control women

Therapy	Cases			Control		
	n (%)	Exposure	Follow-up	*n* (%)	Exposure	Follow-up
Estradiol only	3,335 (22.2)	8.3 ± 5.7	9.0 ± 4.1	5,167 (11.6)	7.1 ± 5.3	9.0 ± 4.2
Any progestin-EPT	5,541 (36.9)	6.5 ± 5.0	8.6 ± 4.2	11,830 (26.7)	5.8 ± 4.4	8.7 ± 4.2
Other/mixed-EPT	3,378 (22.5)	4.8 ± 4.1	7.1 ± 4.3	6,926 (15.6)	4.4 ± 3.8	7.4 ± 4.3
NETA-EPT	1,220 (8.1)	5.8 ± 5.0	7.7 ± 4.3	2,526 (5.7)	4.9 ± 4.2	7.8 ± 4.2
MPA-EPT	707 (4.7)	6.9 ± 5.4	8.5 ± 4.0	1,914 (4.3)	5.9 ± 4.7	8.7 ± 4.1
Levo-IUD-EPT	133 (0.9)	3.0 ± 2.2	4.9 ± 2.9	290 (0.7)	2.9 ± 2.0	5.3 ± 3.3
Tibolone	103 (0.7)	2.1 ± 1.7	4.6 ± 2.9	174 (0.4)	2.1 ± 1.7	4.5 ± 3.0
Vaginal estradiol only	910 (6.1)	2.1 ± 2.2	5.4 ± 4.1	1,765 (4.0)	2.3 ± 2.2	6.5 ± 4.0

EPT estrogen–progestin hormone therapy, *NETA* norethisterone acetate, *MPA* medroxyprogesterone acetate, *Levo-IUD* levonorgestrel-releasing intrauterine device

(odds ratio [OR]; 95% confidence incidence, CI) was assessed with a conditional logistic regression analysis. Subgroup analyses were carried out in women with ET, NETA-EPT, MPA-EPT, Levo-IUD-EPT, other/mixed-EPT-ET, and local vaginal estradiol. Separate sub-analyses were carried out for women who had started the use of HT at and under or over 55 years of age, and also for HT exposures lasting under 3 years, 3–5 years, and over 5 years.

Permissions

The appropriate permissions for the study were obtained from the National Institute of Health and Welfare (THL/1370/5.05.00/2010), the Finnish National Population Register (901/410/14), and the Social Insurance Institution of Finland (KELA 40/522/2010) after receiving a positive statement from the Data Protection Ombudsman, as required by the legislation.

Results

The age at the time of SUI operation was under 60 years of age in 42.0%, between 60 and 69 years in 35.1%, and in the rest (22.9%) over 70 years of age. The cases and controls were evenly distributed among the 18 surgery units.

The cases had used any HT more often than the controls (65.2 vs 42.3%, $p < 0.005$). The difference was the largest for ET (22.2 vs 11.6%, $p < 0.005$), but also various EPTs, tibolone, and vaginal estradiol had been used more often ($p < 0.005$) by the cases than by the control women (Table 1).

The exposure times to various HT regimens and the follow-up times were comparable between the cases and control women (Table 1).

The use of any HT associated with a significantly increased risk for SUI (OR 3.0, 95% CI: 2.9–3.1). The ET regimen carried the highest SUI risk (OR 3.8, 95% CI: 3.6–4.0), which was significantly higher than that for EPT (OR 2.7, 95% CI: 2.6–2.9) (Table 2). The use of NETA- EPT alone was accompanied by a higher SUI risk elevation than that of MPA-EPT alone (Table 2). Also, the uses of tibolone or Levo-IUD-EPT were accompanied by SUI risks, in addition to vaginal estradiol only (Table 3).

Hormone therapy exposure shorter than 3 years was already related to increased risk for SUI, and the extension of exposure to over 5 years showed a further increase (Table 3).

Age over 55 years at the initiation of HT was accompanied by higher elevations in SUI risk than the initiation age of under 55 years (Table 4).

Discussion

We found in this large case–control study that all forms of HT were accompanied with consistent two to three-fold elevations in SUI risk. This risk elevation appeared already within the first 3 years of HT use, and increased further with over 5 years of use. The rise in SUI risk was also related to the woman's age at HT initiation, as starting age above 55 years showed a significantly higher SUI risk than starting age under 55 years. Moreover, there were marked differences in risk between various HT regimens. The SUI risk in users of Levo-IUD-EPT or tibolone must be interpreted with caution owing to the low number of women using these regimens.

There are hardly any clinical data on the effect of estradiol-based HT regimens on the SUI risk; therefore, our findings must be compared with those obtained with CEE and CEE + MPA regimens. The oral use of CEE alone (5,422 women) for 1 year doubled the SUI risk in women who were continent before the start of the treatment [8]. In our study, the 3-year shorter use of estradiol was accompanied by a 2.5-fold and over 5-year use with a more than 4-fold rise in SUI risk. The

Table 2 The rate (*n*, %) and odds ratios (ORs) and 95% confidence interval (95% CIs) for stress urinary incontinence in women using various hormone therapies in relation to women without any hormone use

Therapy	Cases *n* (%)	Control *n* (%)	OR (95% CI)	*p*
No use	5,216 (34.8)	25,627 (57.7)	1.00	
Estradiol only	3,335 (22.2)	5,167 (11.6)	3.8 (3.6–4.0)	< 0.005
Any progestin-EPT	5,541 (36.9)	11,830 (26.7)	2.7 (2.6–2.9)	< 0.005
Other/mixed-EPT	3,353 (31.4)	6,849 (18.5)	2.8 (2.7–3.0)	< 0.005
NETA-EPT	1,207 (11.3)	2,494 (6.7)	2.8 (2.5–3.0)	< 0.005
MPA-EPT	702 (6.6)	1,889 (5.1)	2.2 (2.0–2.4)	< 0.005
Levo-IUD-EPT	132 (1.2)	288 (0.8)	2.2 (1.8–2.8)	< 0.005
Tibolone	103 (1.0)	173 (0.5)	3.4 (2.6–4.5)	< 0.005
Vaginal estradiol only	910 (6.1)	1,765 (4.0)	2.7 (2.5–3.0)	< 0.005

use of CEE + MPA (8,506 women) for 1 year was associated with an 87% increase in SUI risk [8], whereas in our study the use of estradiol in combination with various progestins for under 3 years was accompanied by 120% and over 5 years by a 220% rise in the SUI risk. There are several explanations for these differences. First, this SUI risk rises [8] reflecting the de novo development of SUI, because women were continent before the start of CEE or CEE + MPA, whereas we do not know if our cases had some minor urinary incontinence already at the initiation of the various HT regimens. Thus, higher SUI risk elevations in our cases than in the comparator study [8] may be partially due to including women with worsening of SUI during the use of HT to the degree that an operation was carried out. This gains support from previous data [8], as present SUI before the start of CEE or CEE+ MPA did indeed worsen by 38% and by 47% respectively. Second, the longer exposure times to estradiol-based regimens in our study may also contribute to higher SUI risk elevations. Third, it is possible that the use of estradiol is related to higher SUI risks than the use of CEE, which shows a number of both estrogenic and anti-estrogenic activities. Fourth, it is possible that not only SUI but also other forms of urinary incontinence were recorded in the previous study [8], in contrast to our study where the preoperative diagnosis of SUI was accurate.

Table 3 The rate (*n*, %) and ORs and 95% CIs for stress urinary incontinence in women using hormone therapy according to the exposure time

Exposure time	Cases *n* (%)	Controls *n*	OR (95% CI)	*p*
≤ 3 years				
Estradiol only	613 (7.5)	1,281 (4.4)	2.5 (2.2–2.8)	< 0.005
EPT	1,603 (15.0)	3,867 (10.4)	2.2 (2.1–2.4)	< 0.005
Vaginal estradiol	713 (4.8)	1,332 (3.0)	1.6 (1.5–1.8)	< 0.005
3 to 5 years				
Estradiol only	448 (5.5)	774 (2.7)	3.2 (2.8–3.7)	< 0.005
EPT	1,024 (9.6)	2,261 (6.1)	2.6 (2.3–2.8)	< 0.005
Vaginal estradiol	120 (0.8)	246 (0.6)	1.5 (1.2–1.9)	< 0.005
> 5 years				
Estradiol only	2,089 (25.4)	2,731 (9.3)	4.7 (4.3–5.1)	< 0.005
EPT	2,870 (26.7)	5,565 (15)	3.2 (3.0–3.4)	<0.005
Vaginal estradiol	77 (0.5)	187 (0.4)	1.3 (1.0–1.7)	0.08

It is a common belief that the vaginal use of various estrogens is accompanied by a reduced risk (26%) of urinary incontinence [7]. One explanation for this benefit is the estrogen-induced improvement of urogenital epithelia [6, 17]. Therefore, vaginal estrogen is commonly prescribed to the women with mild symptoms of urinary incontinence and SUI-induced prescribing of vaginal estradiol could at least partially explain the SUI risk elevations in women who had used solely vaginal estradiol in our study. This explanation is supported by our data showing that the SUI risk elevations were the highest for women who had used vaginal estradiol for the shortest time periods, and in fact, in women using vaginal estradiol longer than 5 years, no significant SUI risk elevation was seen.

To our knowledge, no previous data exist for the SUI risk in ET users carrying a Levo-IUD. Therefore, it was a novel finding that this HT regimen was also accompanied with a 2.2-fold SUI risk. Similarly, a new finding is our observation that tibolone use is associated with SUI risk elevation. These regimens operate through the same estrogen and/or progestin receptors in the pelvic floor as do the other forms of HT [18]; therefore, the SUI risks accompanying ET+ Levo-IUD or tibolone could be expected. However, these study groups, although large enough to produce statistical differences in SUI risk, were so small that conclusions of their impact on SUI risk must be drawn with caution.

We can only speculate on the biological mechanisms by which various types of HT might increase the SUI risk. Estrogens are known to stimulate collagenase activity via matrix metalloproteinase activation [19], which may lead to degradation of total collagen, and particularly to that of the most important supportive collagen type I, which is replaced by weaker immature collagen [20]. Indeed, in postmenopausal

Table 4 The rate (*n*, %) and ORs and 95% CIs for stress urinary incontinence in women starting the various hormone therapies under or above 55 years of age

Starting age	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	*p*
< 55 years				
Estradiol only	2,892 (22.0)	4,534 (11.0)	3.6 (3.4–3.8)	< 0.005
EPT	4,916 (37.4)	10,667 (25.9)	2.6 (2.5–2.7)	< 0.005
Vaginal estradiol	147 (1.1)	388 (0.9)	2.0 (1.6–2.4)	< 0.005
≥ 55 years				
Estradiol only	412 (6.2)	561 (2.1)	5.0 (4.2–6.0)	< 0.005
EPT	584 (8.8)	1,014 (3.9)	3.7 (3.3–4.3)	< 0.005
Vaginal estradiol	733 (11.0)	1,253 (4.8)	3.3 (2.9–3.7)	< 0.005

women with SUI, estradiol has been shown to decrease the total amount of vaginal collagen [19]. It is possible that during fertile life, this phenomenon does not cause any clinical consequences, perhaps because of marked cyclic fluctuations in estrogen levels or to some so far unknown compensatory hormonal mechanisms. The only exception is pregnancy, when circulating levels of both estrogens and progesterone are high, and they, together with relaxin, soften the pelvic floor. It is possible that constantly elevated levels of estrogens in postmenopausal women, as in pregnancy, weaken the pelvic supporting structures to the degree that SUI ensues. Furthermore, progestins may potentiate the estrogen activity in the pelvic floor, and NETA may be stronger in this aspect than MPA at explaining why NETA-EPT is accompanied by a higher SUI risk elevation than MPA-EPT in our study. All these estradiol-mediated effects in the pelvic floor may cause and/or worsen SUI in postmenopausal women.

We readily admit a number of weaknesses in our study. First, our study lacked a placebo group; thus, a HT prescription bias may have occurred. Severe vasomotor symptoms are a primary cause of HT use, and they are hardly connected to SUI. In contrast, a pre-existing SUI may have led to a more common use of vaginal estradiol, as discussed above. This SUI-induced bias in the use of vaginal estradiol may account for the increased SUI risk we report for vaginal estradiol. Moreover, it is possible that women having been operated on for SUI after failed primary SUI surgery were more likely to use HT, but the proportion of such cases must be small in view of the 87.2–91.3% success of primary SUI surgeries in Finland [21]. Second, hysterectomy is associated with a 23% risk increase for SUI [22], but we could not match the cases and controls with regard to hysterectomy. Judging from the higher rate of ET use in SUI cases (22.2%) compared with controls (11.6%) we may assume that the likelihood of hysterectomy was two-fold in the cases. As we detected a 3.8-fold SUI risk in ET users, it is likely that the use of ET also caused de novo SUI and/or worsened SUI in the hysterectomized women. Third, we could not assess if patients were continent or incontinent before the start of HT, and thus our data express the combined risk for de novo development and worsening of SUI during the use of HT. It is also possible that some patients had suffered from mixed incontinence. However, these were likely stress-dominant, because they were operated for SUI. Fourth, it is possible that both cases and controls included women with SUI who did not want any surgery; however, such a chance is small in view of the troublesome symptoms of SUI and almost free medical care in Finland. Finally, although we could match the cases and controls for the most important confounding factors, we could not do it with regard to bodyweight, which is a risk factor for SUI [23]. However, clinical data imply that overweight women are less likely to start the use of HT, and this would reduce any errors of SUI risks possibly linked to overweight women.

As the strengths of our study, we first emphasize the large size of the study population. Second, with SUI operation as the end-point, we are confident that our patients truly had SUI. Third, we could assess and compare the impact of various estradiol-based regimens, which have been much less frequently studied in this field of research than CEE-based therapies. Fourth, our data on Levo-IUD-EPT and tibolone are novel. Finally, we are also convinced that the history of HT use preceding SUI operation is accurate, as it is based on comprehensive nationwide register documentation.

Modern guidelines for the optimal prescription of HT advocate the use of HT to improve the quality of life in women with severe vasomotor symptoms [24]. This requires a careful, individual evaluation of the benefits and risks of HT. Our data show that systemic estradiol-based HT regimens and tibolone may predispose to the development and/or worsening of SUI. Therefore, their use must be considered with caution, at least in women who already have mild SUI or who have major SUI risk factors.

Compliance with ethical standards

Conflicts of interest PR-S has received funding for congress attendance from Johnson & Johnson and Astellas Pharma. HS-P has been a speaker for Mylan and received funding for congress attendance from Mylan and MSD. TM has been a speaker and/or received consulting fees from Mylan and Astellas Pharma.

MG and OY have nothing to disclose. FH and PV work for EPID Research. EPID Research is a company that performs financially supported studies for several pharmaceutical companies.

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