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From systemic hormone therapy to vaginal estrogen – A nationwide register study in Finland, 2003–2012

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ABSTRACT

Objectives: To assess the patterns of use of reimbursed systemic hormone therapy (HT) and vaginal estrogen preparations among women aged 45 and older in Finland.
Study design: Reimbursed purchases of prescribed systemic HT and vaginal estrogen preparations for the years 2003–2012 were obtained from a nationwide prescription registry. Systemic preparations included estrogen patches, gels and tablets, tibolone, continuous combination preparations and sequential combination preparations. Prescribed vaginal estrogens included a vaginal ring and vaginal tablets.
Main outcome measures: Annual period prevalence for systemic HT and vaginal estrogen use.
Results: The total prevalence of prescribed HT use remained relatively constant (at 26–27%) throughout the studied period, but the share of women using systemic preparations decreased from 21% to 12%, while the share of women using vaginal estrogens increased from 9% to 19%. Decreases were observed for all classes of systemic preparations, although the decrease was largest for sequential combination preparations (from 4.9% to 1.6%) and estrogen tablets (from 5.2% to 2.9%). Continuous combination preparations remained the most commonly used types of systemic preparation (5.4–4.2%). Systemic HT use decreased most among 45–49 year old women (9.5–4.3%), while the use of vaginal estrogens increased most among those aged 65 and over.
Conclusions: Based on the register data, the trends in HT use indicate changed prescribing patterns in accordance with clinical guidelines. It is notable that since 2009, vaginal estrogen was more commonly prescribed than systemic HT.

1. Introduction

In 2002–2003, the Heart and Estrogen/Progestin Replacement Study (HERS) [1], followed by the Women's Health Initiative (WHI) [2] and the Million Women Study (MWS) [3], revealed an increase in the risks of breast cancer, coronary vascular disease, stroke and thromboembolic events associated with systemic hormone therapy (HT) in postmenopausal women. As a result of these trials, clinical guidelines were revised and the recommended indications were limited to low-dose, short-term treatment of menopausal symptoms and the prevention of osteoporosis in patients with postmenopausal symptoms or for those whom other treatments for osteoporosis are contraindicated. Vaginal estrogens were recommended for the treatment of urogenital symptoms [4–7]. In Finland, a national consensus conference was held in 2004 in order to unify the clinical management of menopausal symptoms [15].

Decreased HT use has been reported in many countries, but comparisons of the magnitude of the changes across countries are challenging due to differences in the included dosage forms and databases being used. According to pharmacy claims data, the prevalence of systemic HT in the United States (US) decreased from 19% to 5% between 2000 and 2009 [13]. Furthermore, based on pharmacy sales data, the prevalence of estrogen-only treatment decreased from 13% to 9% and that of systemic combination preparations from 15% to 8% between 1999 and 2002 [8]. In Spain, among women attending a breast cancer screening programme, the prevalence of prescribed HT (without knowledge of the type) decreased

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Table 1
Percentage of women aged 45 years or older with purchases for reimbursed systemic hormone therapy and vaginal estrogen preparations in Finland in 2003, 2006, 2009 and 2012.

	2003			2006			2009			2012		
	Systemic	Vaginal	All	Systemic	Vaginal	All	Systemic	Vaginal	All	Systemic	Vaginal	All
45–49	9	2	11	7	3	9	5	3	8	4	3	7
50–54	32	6	35	24	9	30	21	12	28	17	12	25
55–59	40	11	46	30	16	41	26	20	40	22	23	38
60–64	33	14	42	25	19	39	21	24	39	17	26	38
65–74	17	13	28	14	18	29	12	23	32	11	27	34
75+	4	7	10	3	9	11	3	13	15	3	17	19
All	21	9	27	16	12	26	14	16	27	12	19	27

the most (11–1.2%) among the youngest women (50–54 years old) between 2002 and 2007, which suggests that the share of women just starting HT decreased as well [14]. These earlier reports suggest that the widespread media coverage of the WHI resulted in rapid changes in the prescribing patterns for systemic HT [8,10]. In a comparison of Northern European countries based on wholesale sales statistics (as defined daily doses, DDD), the use of estrogens (G03C) alone or in combination with progestogens (G03F) decreased less in Finland (25% between 2001 and 2005) than in Sweden (61% between 1998 and 2005), Norway (51% between 1999 and 2005) and Iceland (43% between 1999 and 2005) from the year of peak HT sales to the year 2005 [12].

In earlier studies, HT use and consumption have often been assessed using register data at the level of the active ingredient. In the Finnish context, these data include prescribed and reimbursed vaginal estrogen. It is therefore less well known how the changes in clinical guidelines have affected the use of systemic HT in Finland. In this study, we examine the patterns of prescribed HT use in Finland during the years 2003–2012 among women aged 45 years or older based on preparation type and age.

2. Methods

Data were retrieved from the nationwide prescription registry at the Social Insurance Institution of Finland (Kela) [11]. The Kela database comprises all reimbursed purchases of medicines used in outpatient care for all permanent residents in Finland. At the time of the study, HT preparations were partly reimbursed by the National Health Insurance (NHI). For these preparations, the reimbursement was 50% coinsurance with a fixed co-payment during the years 2003–2005 and 42% coinsurance without a fixed co-payment between 2006 and 2012. The price exceeding the coinsurance was paid by the patient. Non-reimbursed medicines are paid for in full by the patient and are not captured by the prescription register.

At the time of the study, systemic HT was reimbursed and available by prescription only. Vaginal estriol creams (two brand names) and vaginal suppositories (two brand names) were available over-the-counter (OTC), and only one of these brand names was reimbursed, when prescribed, until 2004. Reimbursed vaginal estradiol tablets and the estradiol ring were available by prescription only.

We extracted all reimbursed purchases of HT preparations in Anatomical Therapeutical Chemical (ATC) groups G03C and G03F for women aged 45 or older for each year [17]. Preparations not intended for use as menopausal hormone therapy according to the summary of product characteristics (SmPC) were excluded. We classified the systemic preparations based on their active ingredient(s) and administration route into estrogen patches, gels and tablets, tibolone, continuous combination preparations (hereafter referred to as combination preparations) and sequential combination preparations (hereafter referred to as sequential preparations). Vaginal estrogen preparations, i.e. vaginal tablets, rings and creams, were classified together (hereafter referred to as vaginal estrogens).

Annual period prevalences of reimbursed HT use were calculated for each HT class using the female population counts obtained from the population register as a denominator. Women were classified as HT users if at least one of the above-mentioned HT prescriptions was dispensed during the course of a single year. Women, who used several types of preparations during a single year were classified as users for each different HT class but only once in the calculation of overall prevalence. Data management and analyses were conducted using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

In 2003, 27% of women aged 45 or older purchased at least one reimbursed hormone therapy preparation (Table 1). In total, 21% purchased systemic HT preparations and 9% purchased reimbursed vaginal estrogens. Ten years later, the prevalence of reimbursed HT use was the same (27%), but the share of women using a systemic and vaginal preparation as a prescription was nearly the reverse: 12% purchased systemic HT, whereas 19% purchased reimbursed vaginal estrogens. Reimbursed vaginal estrogens became more commonly used than systemic HT preparations in 2009.

Similar patterns were observed for all age groups during the studied period (Table 1). Overall, 11% of 45–49 year old women used HT in 2003 and 10% used systemic HT. By 2012, the share of systemic HT users in this age group decreased to 4%, while the overall share of HT users decreased to 7%. Among women aged 50–54 years, the prevalence of reimbursed vaginal estrogen use doubled from 6% to 12% and the prevalence of systemic HT use decreased from 35% to 17%. Total HT use remained common (46%) among women aged 55–59 years, but the share of systemic HT users decreased from 40% to 22% and the share of reimbursed vaginal estrogen users increased from 11% to 23%. Among 60–64 year old women the share of HT users decreased only slightly, but reimbursed vaginal estrogen was more commonly used than systemic HT after 2009. In the oldest age groups, the increase in the use of vaginal estrogen resulted in an overall increase in HT use, even though the share of women using systemic HT decreased. Among 65–74 year olds, the total prevalence grew from 28% to 34%, while among those aged 75 or older it grew from 10% to 19%.

The use of all different types of systemic HT decreased between 2003 and 2012 (Fig. 1). Combination preparations (5.4–4.2%) and estrogen tablets (5.2–2.9%) retained their place as the most prevalent systemic HT preparations throughout the study period. The use of combination preparations decreased the least, by 23.4% between 2003 and 2012. In contrast, sequential preparation use decreased the most, by 67.7% (from 4.9% to 1.6%). Estrogen patches (3.0–1.4%) and tibolone (1.6–0.7%) were used the least in the years 2003–2012. Apart from estrogen gel purchases (2.9–1.7%), which increased between 2007 and 2008, a constant decreasing trend was observed for all systemic HT.

An examination of different types of preparations by age group in 2003 and 2012 shows that the overall use of systemic HT

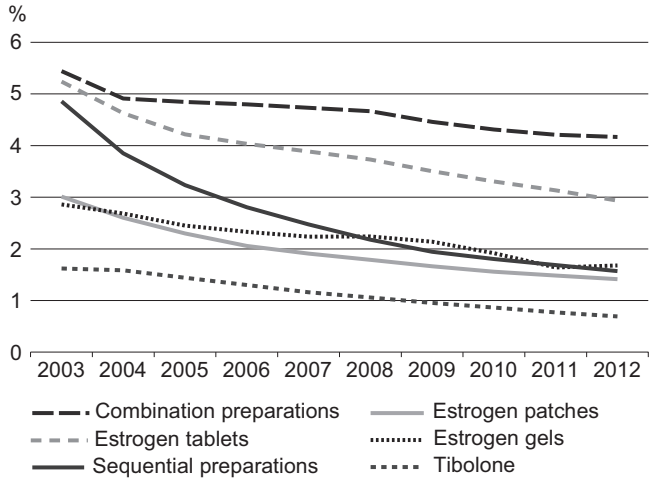

Fig. 1. Percentage of women aged 45 years or older with purchases for different types of reimbursed systemic hormone therapy preparations in Finland during 2003–2012.

decreased in all age groups apart from that of the oldest, those over 90 year of age, who rarely used HT (Fig. 2). The use of systemic HT was most prevalent among 56-year-old women (2003: 41%, 2012: 23%), while the decline in the prevalence was largest among 57 year olds, from 41% to 22%. In 2003, the prevalence of systemic HT was at least 40% among women aged 56–57 years, at least 30% among women aged 52–63 years and at least 20% among women aged 50–68 years. In 2012 the prevalence of systemic HT was less

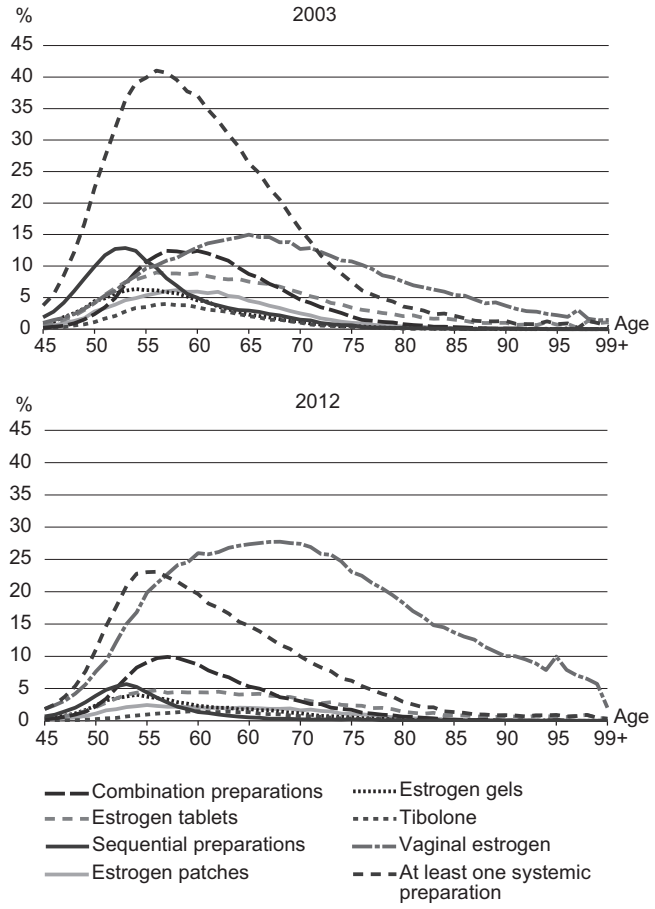

Fig. 2. Percentage of women with purchases for different reimbursed systemic HT and vaginal estrogen preparations in Finland by age in 2003 and 2012.

than 30% in all 1-year age groups and more than 20% among women aged 53–59 years. Vaginal estrogen was used by less than 15% of women in all age groups in 2003. In 2012, the prevalence was at least 15% in 1-year age groups between 53 and 82 years of age.

The use of vaginal estrogen increased in all age groups, and the largest absolute increase was among 70-year-old women (from 13% to 27%). In 2003, vaginal estrogen was more commonly used than systemic HT among women aged 72 years and older, whereas in 2009 it was more common in all age groups over 60 years of age. The notable increase in the share of women using vaginal estrogen among women aged 65 and older was the reason that the overall prevalence of HT use increased in this age group.

Sequential preparations, typically used by younger peri- and menopausal women, were most prevalent among women aged 52–53 years in 2003 (12.7% and12.9%, respectively) and in 2012 (5.3% and 5.7%), and the absolute decline in prevalence (−7.4%) was largest in this age group as well. The prevalence declined by at least −5% among women aged 49–57 years. Combination preparations were used most often by women aged 57 years (from 12.4% to 9.9%), while their use declined most among women aged 62 years (from 11.4% to 7.2%). Their prevalence declined by at least −3% among women aged 60–66 years. Tibolone use was most common among women aged 57 years in 2003 and among women aged 60 years in 2012. The prevalence declined most, by −2.8% (from 4.0% to 1.2%), among 57 year olds and by at least −2% (from 2.8–4.0% to 0.7–1.2%) among women aged 53–59 years.

The one-year age group with the highest share of users for estrogen tablets/gels in 2003 and 2012 was 56 year olds (from 9.0% to 4.8%) and 54 year olds (from 6.4% to 4.0%), respectively. Estrogen patches were used most often by 58 year olds in 2003 (6.2%) and 55 year olds in 2012 (2.5%). The prevalence declined the most for estrogen tablets/gels/patches in the 1-year age group of 57 year olds (−4.5%)/58 year olds (−2.8%)/58 year olds (−4.0%), respectively. The prevalence of estrogen tablet use declined by at least −3% among women aged 52–67 years, while the prevalence of estrogen patch use declined by at least −2% among women aged 52–66 years and the prevalence of estrogen gel use declined by at least −2% among women aged 52–61 years.

4. Discussion

The prevalence of reimbursed HT use among women aged 45 years and older remained similar (27%) between 2003 and 2012, but the use progressively shifted from systemic preparations to reimbursed vaginal estrogens. The prevalence of systemic HT use decreased from 21% to 12%. Overall, the use of reimbursed HT increased among women aged 65 years and older and decreased among younger women. The use of reimbursed systemic HT decreased in all age groups, whereas the use of vaginal estrogen increased in all groups.

Systemic HT use increased continuously in the 1990s and peaked around the year 2000, when HT was widely used to relieve menopause symptoms and prevent osteoporosis and coronary heart disease [8,10,21–24]. The findings from our study are in line with the results of a database study from Finland reporting a decline in the use of systemic estrogen preparations between 2002 and 2005 and an increase in the use of vaginal estrogens between 2000 and 2005 [18]. In the US, Steinkellner et al. [13] reported a continuous decline in systemic HT use, from 22% in 2000 to 9% in 2009, which is in accordance with our study results. Similarly in Steinkellner's study, treatment regimens shifted to favour prescribed vaginal estrogen, which became the most predominant formulation for women initiating therapy in 2006, whereas in our study the shift occurred slightly later, in 2009. However, the increase in vaginal estrogen reported by Steinkellner et al. (from

2% in 2000 to 3% in 2009) was not as remarkable as the increase reported in our study (from 9% in 2003 to 19% in 2012). Apart from the study by Steinkellner et al., to the best of our knowledge the relative shift to vaginal estrogen has not been previously reported. Hersh et al. [10] noted in their analysis in 2004 that prescriptions for vaginal formulations did not decline in the years 2002–2003; however, the prevalence in their study remained quite low overall. As far as we know, we do not have information from other countries regarding to vaginal estrogen use.

According to our results, the prevalence of reimbursed vaginal estrogen use increased in all age groups between 2003 and 2012. Based on IMS Health Sales statistics (01/2014), the market share of reimbursed vaginal estrogens was 32–54% (2004–2011) of the total vaginal estrogen preparations sales in Finland measured in days on therapy (DOT: a measure of sales with a set average daily dose that takes into account the package size and volume of the preparation). The market share of OTC vaginal estrogen sales thus decreased from 68% in 2004 to 46% in 2011. This decline might partly be due to women shifting from OTC preparations to reimbursed vaginal estrogen prescribed by a physician. Physicians might offer reimbursed vaginal estrogen more often as an alternative to systemic HT while discussing possible discontinuation of systemic HT and thus women might start vaginal estrogen more compliantly. The increased prevalence of reimbursed vaginal estrogen might also be a consequence of the fears and worries related to systemic HT use [25]. In a Finnish questionnaire survey, half of all systemic HT users reported experiencing fears (50%) and adverse reactions (6%). The most common fear was breast cancer (26%) [25], similarly to the results from the European Menopause Survey (2006) [26]. One-third (35%) of the respondents using systemic HT had considered discontinuing HT, while a little over a third (40%) had temporarily discontinued the use of HT. The use of vaginal estrogen provides topical effects with minimal systemic absorption [16]. While vaginal estrogen users experienced an improvement in their vaginal mucosa (88%), they also reported fears related to HT (44%) [25].

Our study shows that prescribing HT is in accordance with current clinical guidelines for menopausal HT in Finland: sequential preparations were most commonly used by young perimenopausal women and combination preparations by postmenopausal women. The largest decline in young users might be related to the revised guidelines, which no longer suggest the prophylactic use of HT, e.g. for the prevention of coronary heart disease and osteoporosis in women without menopausal symptoms [15]. The use of combination HT did not change notably during the decade under study; instead, women aged 55–65 years continued using HT similarly as before.

According to the Finnish guidelines, the criteria for choosing different HT preparations are related to the practicality of use of the chosen dosage form [16]. Estrogen patches and gels are considered less harmful with respect to the patient's thrombotic risk [27,28]. Nevertheless, our results show that the use of estrogen patches and gels decreased in a similar trend with respect to estrogen tablets and did not exceed their use rate once during the 10-year study period. Yet, estrogen gels are the only systemic preparations for which use rates increased at one point during the study period. It is also recommended that HT be started with a low dose of estrogen and that the dose be adjusted based on the clinical response and adverse-effects [16], which may be easy to implement with self-adjustable estrogen gel. In the present study, estrogen gels were most used by women under 55 years of age, which supports this finding. Also, according to the Finnish guidelines [16], combination HT can be implemented with an IUD or progestin tablets combined with a low dose of estrogen, which in our results most often was tablet or gel. Only half a per cent of all women aged 45 and older in Finland used an IUD during the years 2008–2012 [11]. Additionally, since women pay for most of the HT purchases themselves, the prices of different preparations may have influenced what form of dosage the women chose, e.g. estrogen tablets over estrogen patches and gels.

The decreased use of systemic HT may have resulted in a number of women receiving inadequate treatment for their menopausal symptoms. According to a Finnish report, half of all postmenopausal women suffer from severe symptoms that affect their everyday life [29]. When considering the public health and societal factors of HT, not treating postmenopausal symptoms has been seen as a bigger risk than the one related to HT. Thus, in 2004 the National Consensus Conference recommended continuing to refund HT preparations [15]. However, these more tolerant attitudes towards HT use were not evident in our study results.

A limitation of our study is that the data do not include all people using vaginal estrogen in Finland. However, IMS Health sales statistics (01/2014) support our data about the prevalence of reimbursed vaginal estrogen increasing. Furthermore, it must be noted that progestogene-only preparations (ATC class G03A) were not included in our study, and therefore the results related to combination therapy only apply to combination products. Thus, the information on how often estrogen gels, patches or tablets are used with a separate preparation consisting of a progestogen tablet or IUD are lacking. Therefore, the total use of combination therapy should not be estimated based on the results of this study. Systemic HT is used on prescription only and nearly all preparations are reimbursed. Therefore the use of systemic HT is well captured by the prescription register.

In conclusion, the trends in HT use indicate changed prescribing patterns in accordance with national and international clinical guidelines. The total share of women aged 45 years or older using reimbursed HT remained similar between 2003 and 2012. However, while prescribing systemic HT decreased, vaginal estrogens became more commonly prescribed in all age groups. Our study clearly shows that comparing HT use between different countries is difficult due to different prescribing and data recording practices. This aspect should be taken into account when planning future studies.

Contributors

E.H. drafted the manuscript and participated in the analysis and interpretation of the data. K.A. and M.T. have contributed to the conception of the data, and designing and revising the manuscript. A.-M.H. involved in designing and revising the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was not needed for this type of the research (National Advisory Board on Ethics: http://www.tenk.fi/ENG/function.htm).

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