

# Use of vaginal estrogen in Danish women: a nationwide cross-sectional study

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## Key words

Estrogen therapy, female urogenital disease, genitourinary syndrome of menopause, hormone therapy, local estrogen therapy

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## Conflicts of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this study.

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## Introduction

The decreased level of estrogen in postmenopausal women leads to urogenital atrophy (1). The atrophy may cause symptoms such as vulvo-vaginal dryness, itching and burning, dyspareunia, recurrent urinary tract infections, and urinary incontinence (2–5). Going untreated, symptomatic urogenital atrophy may lead to sexual dysfunction and overall lowered quality of life (2,6–10). Though current knowledge shows vaginal estrogen to be an effective and safe treatment of urogenital atrophy (11–13), studies suggest that many symptomatic women are left untreated (2,3).

## Abstract

**Introduction.** We know little about the use of vaginal estrogen in perimenopausal and postmenopausal women. We aimed to assess the prevalence of vaginal estrogen use in Denmark. **Material and methods.** The study was designed as a nationwide cross-sectional study of all Danish women aged 40–79 years, living in Denmark during the period 2007–2013. The Danish Prescription Register delivered data permitting us to assess the prevalence, age and regional geographical belonging of women purchasing prescribed vaginal estradiol. The number of women using over-the-counter vaginal estriol products was estimated from sale statistics from the same register. **Results.** In 2013, 10.2% of all Danish women between 40 and 79 years of age used vaginal estradiol. The prevalence of women using this type of vaginal estrogen increased from 8.5% in year 2007 to 10.2% in 2013. The use peaked at 16.5% in women aged 60–74 years. The vaginal tablet was purchased more than the vaginal ring. We found no relevant difference in use between the five regions of Denmark. Taking the sale of vaginal estriol into account, the prevalence of vaginal estrogen use in 2013 could be estimated to a total of 12.1%. **Conclusions.** Comparing our result to the prevalence of urogenital atrophy-related symptoms reported in the literature, our study suggests an under-diagnosis and under-treatment of this condition. Teaching women and primary-care physicians about symptomatic urogenital atrophy and its treatment options may increase the quality of life for many women.

**Abbreviations:** ATC, Anatomical Therapeutic Chemical; DDD, Defined Daily Dose.

The increasing life expectancy for women around the world and the thereby increasing prevalence of symptomatic urogenital atrophy makes it important

## Key Message

The study shows the prevalence of vaginal estrogen use among perimenopausal and postmenopausal Danish women. Comparing our results to studies reporting the prevalence of symptoms related to urogenital atrophy, this study suggests a large under-diagnosis and under-treatment of the condition.

to be aware of diagnosis and treatment of the condition.

In Denmark, a large majority of women using vaginal estrogen obtain a prescription for this treatment (14). Therefore, most of the Danish women using vaginal estrogen are registered in the Danish Prescription Register, providing an opportunity to assess the use of vaginal estrogen in Denmark according to age and residence.

The aim of this nationwide cross-sectional study was to assess the prevalence of perimenopausal and postmenopausal women using vaginal estrogen.

## Material and methods

We included women between 40 and 79 years of age living in Denmark during the period 2007–2013. The age and geographical region of each woman in the study population were extracted from the National database StatBank Denmark (<http://www.statistikbanken.dk>; 02-04-2015).

During the period 2007–2013, options for vaginal estrogen included vaginal estradiol tablets/ring and vaginal estriol cream/suppositories. The purchase of vaginal estradiol needs a doctor's prescription. Therefore, women using vaginal estradiol are registered by social security number in the Danish Prescription Register ([medstat.dk](http://medstat.dk); 02-04-2015). Vaginal estriol, on the other hand, is bought over the counter. Women using vaginal estriol are therefore not registered anywhere. However, information about the amount of both sold vaginal estradiol and vaginal estriol is available in the Danish Prescription Register. Sold vaginal estrogen is calculated in Defined Daily Dose (DDD) units.

By searching for the Anatomical Therapeutic Chemical (ATC) code (G03CA03) and the product names of vaginal estradiol preparations in the Danish Prescription Register, we were able to assess the number of women in our study population using vaginal estradiol as well as the amount of sold vaginal estradiol in DDD units. We were also able to assess the age and geographical region of these women. In the prevalence assessment, women were categorized as users if they had at least one prescription of estradiol. In the comparison of the popularity of each preparation type, several prescriptions in the same woman were all included.

By searching for the ATC code for vaginal estriol (G03CA04) and the product names of these preparations, we were only able to assess the number of DDD units sold, not the number of women using this type of vaginal estrogen. However, by knowing the number of women using vaginal estradiol and the corresponding number of DDD units, we were able to estimate the yearly number of DDD units of vaginal estrogen used per woman. By dividing the number of sold DDD units of vaginal estriol

with the estimated yearly dose used per woman, we were able to estimate the number of women using vaginal estriol.

The study was approved by the local Ethics Research Committee of the Capital region of Denmark (H-4-2013-105).

## Statistical analysis

All statistical analyses were carried out using SPSS (SPSS Inc., Chicago, IL, USA). Kolmogorov's test and Levene's test were used to show a nonparametric nature of data. The correlation of Spearman's rho,  $r_s$ , was used in the analysis of the data. All  $p$ -values are two-sided. Some data are presented as mean  $\pm$  standard deviation.

## Results

Of the 1 339 829 women between the ages of 40 and 79 years living in Denmark in 2013, 10.2% used vaginal estradiol. The prevalence of women using this type of vaginal estrogen increased significantly throughout the study period ( $p < 0.01$ ) (Figure 1).

The prevalence of women using vaginal estradiol was highest among women in the age group 60–74 years (Figure 2). During 2007–2013, the prevalence of usage of this type of vaginal estrogen increased significantly for the age groups  $> 60$  years ( $p < 0.01$ ) but decreased slightly – although significantly – for women in the age group 40–49 years ( $p < 0.01$ ).

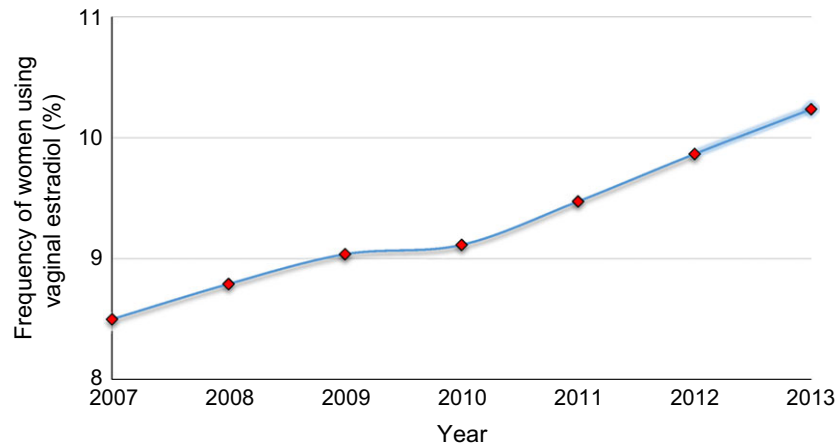
Vaginal estradiol tablets were more popular than the vaginal estradiol ring. Of all the vaginal estradiol purchased, tablets constituted  $96.0 \pm 0.6\%$ , and this proportion did not change with increasing age or over time.

As shown in Figure 3, the use of vaginal estradiol was similar in the five regions of Denmark in the study period 2007–2013, although the Capital Region of Denmark had a slightly higher use than the other regions. The prevalence of women in vaginal estradiol therapy increased significantly in all regions during the study period ( $p < 0.01$  in each region).

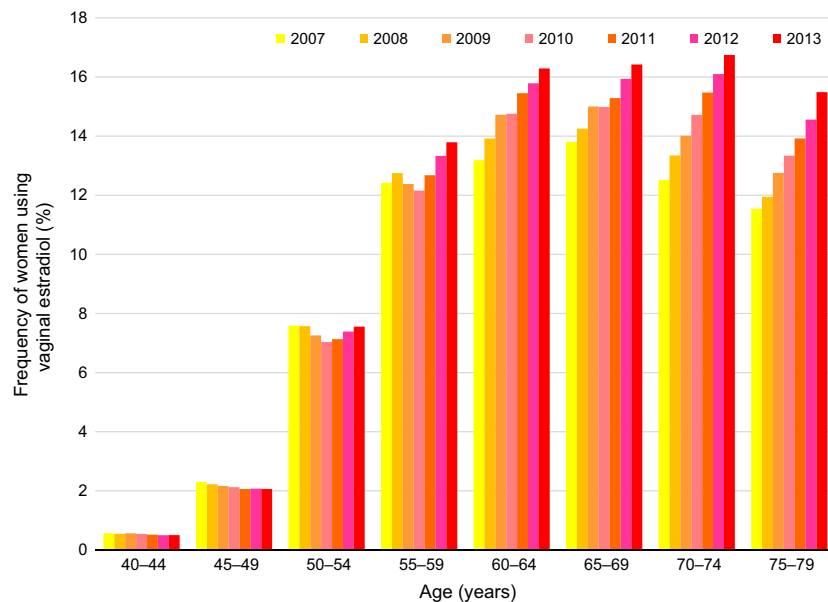
In the year 2013, the volume of vaginal estrogen sold was  $11 \times 10^6$  DDD units estradiol and  $2 \times 10^6$  DDD units estriol (Figure 4). Knowing that the  $11 \times 10^6$  DDD units estradiol account for 10.2% of the study population, the total prevalence of vaginal estrogen users in 2013 can be estimated to be 12.1% .

## Discussion

The prevalence of perimenopausal and postmenopausal women using vaginal estrogen in 2013 was about 12.1%. The use of vaginal estradiol increased from 8.5% to



**Figure 1.** This figure shows the significant increase in vaginal estradiol use among 40–79-year-old women in the Danish population in 2007–2013.



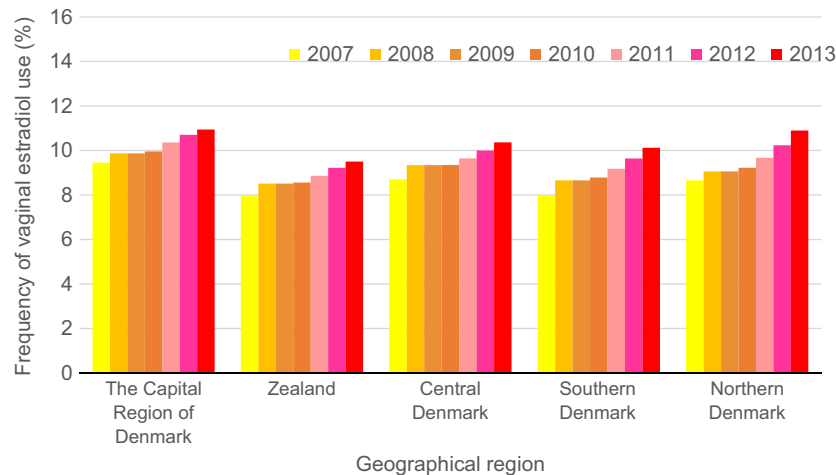
**Figure 2.** The figure outlines the use of vaginal estradiol according to the age of the women. Women between 60 and 74 of age use the drug the most in all years investigated.

10.2% from 2007 to 2013, peaking at 16.5% in women aged 60–74 years, and with little variation between the regions in Denmark.

Many studies have investigated the frequency of urogenital symptoms among women in perimenopause, menopause, and postmenopause. The studies have different study populations and outcome measures. This is reflected in the different frequencies of symptomatic urogenital atrophy reported by the studies. An online survey of 4264 women aged 55–65 years living in one of five countries found a prevalence of 39% of urogenital symptoms including vaginal dryness/itching, dyspareunia, and urinary

incontinence (2). Another online survey study of only vulvovaginal symptoms in American women aged 45–89 years showed a prevalence of 45% (10). A cross-sectional analysis based on 98 705 American women aged 50–79 years reports a prevalence of 41% of urogenital symptoms (15). Of all urogenital symptoms, Barnabei et al. only looked at vaginal dryness and “genital irritation”. They found a prevalence of 26% and 10%, respectively, in a population of 2763 women aged 55–88 years (16).

We found that only 12.1% of 40- to 79-year-old Danish women use vaginal estrogen, the highest prevalence being 16.5% in the age group 60–74 years. Comparing



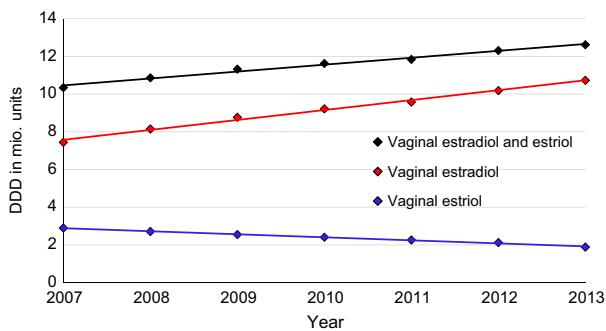
**Figure 3.** A significant increase in the use of vaginal estradiol among women in all regions of Denmark. The prevalence of usage is slightly larger in the Capital Region of Denmark.

our result with the prevalence of symptoms reported in the literature, our study seems to suggest an under-diagnosis and under-treatment of symptomatic urogenital atrophy. This is supported by Nappi and Kokot-Kierepa (2), who demonstrated that 63% of symptomatic postmenopausal women never received treatment for their urogenital symptoms.

In the VIVA study by Nappi and Kokot-Kierepa (3), 500 Danish postmenopausal women participated in an international survey of urogenital symptoms. The paper does not specify the prevalence of symptomatic urogenital atrophy specifically in the Danish participants, but the total prevalence among the 3520 participating women was 45%. However, the study specifies that about 35% of the Danish women with urogenital symptoms did not seek help from a healthcare professional. Most of those who did went to their primary-care physician. Only 27% of those seeking help visited a gynecologist. Of the Danish

women, 51% claimed that their primary-care physician never raised the issue of postmenopausal vaginal health. Furthermore, 43% of the Danish women had negative associations with vaginal estrogen treatment, thinking that the treatment has the same risks of adverse effects as systemic hormone replacement therapy. These findings may explain the under-diagnosis and under-treatment suggested by our results. Believing that vaginal estrogen therapy has the same risks of adverse effects as systemic therapy can be a rational reason for not seeking treatment for symptomatic urogenital atrophy. Additionally, when most help is sought from primary-care physicians, where less awareness of the condition may be expected compared with more specialized parts of the healthcare system, under-diagnosis and under-treatment could easily happen.

The increase in use of vaginal estrogen through the study period may be due to a combined effect of an increased awareness of the possible impact from vaginal estrogen on urogenital symptoms and a general wish to replace systemic hormone therapy with local treatment after concerns were raised by articles published about 10 years ago (17–19), anticipating that local treatment has less impact on cancer risk than systemic treatment. Educating healthcare professionals and women about symptomatic urogenital atrophy would likely raise the prevalence of vaginal estrogen usage among postmenopausal women even more. Further research on the safety of vaginal estrogen is therefore needed to properly inform all people.



**Figure 4.** The volume of sold vaginal estrogen in Denmark in the years 2007–2013. The volume is counted in Defined Daily Dose and is shown for both the prescription-demanding vaginal estradiol as well as vaginal estradiol, which can be bought over the counter.

## Conclusion

Many postmenopausal women seem to have untreated symptomatic urogenital atrophy. Educating women and

primary-care physicians about urogenital atrophy could reduce the under-diagnosis and under-treatment of this condition and thereby enhance the quality of life of many women around the world.

## Funding

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