ELSEVIER

Maturitas 31 (1999) 241–247

MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL

Finnish physicians' opinions of vaginal estriol in self-care

Elina Hemminki *, Sinikka Sihvo

National Research and Development Centre for Welfare and Health, Health Services Research Unit, P.O. Box 220, 00531 Helsinki, Finland

Received 16 September 1998; accepted 2 February 1999

Abstract

Objective: In Finland vaginal estriol drugs became available without prescription in 1992, resulting in widespread advertising of these drugs to lay women and in an increase in sales. The purpose of this study was to find out what Finnish physicians think about the fact that vaginal estriol does not require a prescription, and if they have found any problems resulting from this. *Methods*: A questionnaire survey was sent to gynecologists and general practitioners ($n = 341$, 77% response rate) in Finland in 1996. *Results*: 60% of the physicians considered vaginal estriol to be suitable for over-the-counter (OTC) status, and to be much more suitable than the other estrogen containing drugs (contraceptive pill and drugs for emergency contraception) we asked about in our study. Opinions varied by specialty, work experience and reported problems relating to OTC status. The most common reasons given for suitability referred to increased access, and those given for unsuitability referred to general dangers of self-care. Of all physicians 12%, and of private gynecologists ($n = 33$) 49% reported having observed problems with the OTC status, mostly in care-seeking and indications; some gynecologists mentioned adverse effects of the drug itself. 39% of the physicians thought that the best person to provide information about vaginal estriol is a physician. *Conclusions*: Pharmacological literature and physicians' opinions suggest a re-evaluation of the role of physician surveillance of vaginal estriol drugs.

Keywords: Vaginal estriol; Over-the-counter; Physicians

1. Introduction

In recent years the treatment of post-menopausal women with estrogens and progestins has become increasingly common [1]. For the atrophy of vaginal and urethral mucosa and prevention of recurrent urinary tract infections [2–4], local therapy with estriol or other estrogens is an option. In some European countries estriol has been switched to over-the-counter (OTC) status so that a physician visit or prescription is not

* Corresponding author. Tel.: +358-9-39672307; fax: +358-9-39672485.
E-mail address: Elina.Hemminki@stakes.fi (E. Hemminki)

0378-5122/99/$ - see front matter
PII: S0378-5122(99)00010-9

required [5,6]. In Finland the status change occurred in 1992, and this resulted in widespread drug advertising to lay women and in an increase in the sales of vaginal estrogens, Fig. 1. Sales of OTC estriol preparations partly replaced previous sales of prescription estriol, and partly it was a real increase. Sales of vaginal prescription estrogens have been notably less than that of OTC estrogens (all estriol), but slowly increasing (2.4 defined daily doses in 1996) [7].

This introduction of local estriol onto the OTC market in Finland did not cause public professional discussion. This is puzzling both from health service and safety perspectives. Vaginal dryness and other urogenital symptoms are common among postmenopausal women, and often these problems are long lasting [8]. The possibility of being able to buy a drug directly from the pharmacy may result in decreased visits to physicians. Locally administered estriol are believed to be safe, but no long-term large-scale epidemiological studies exist. Estriol, like other estrogens, is absorbed well by the vaginal mucosa and causes a prolonged increase in plasma estriol concentrations [3,9–12]. Vaginally administered estriol, even in the recommended low dosages, has systemic effects [3,12,13]. Even though estriol has poorer affinity for endometrial estrogen receptors than for those in the vaginal and urethral mucosa, vaginal estriol has estrogen effects on the uterine endometrium and myometrium [12,13], and endometrial hyperplasia, even though of unclear causality, has been reported [2,14]. Endometrial hyperplasia has been reported to frequently occur after oral estriol [15]. We found no epidemiological literature on the effect of local estriol on other estrogen sensitive organs such as breasts. In a trial with 12-week treatment period with estriol pessaries, two women out of 53 reported breast enlargement or pain [16].

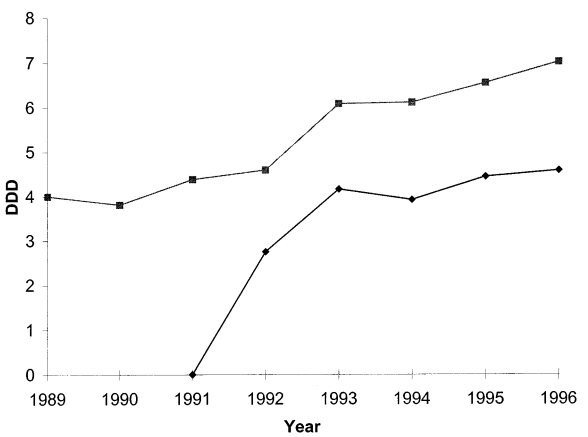

Fig. 1. Total sales of vaginal oestrogens (top line) and sales of drugs available without prescription (lower line) in Finland in 1989–1996, defined daily doses (DDD) per 1000 inhabitants. Source: unpublished data from the Finnish National Agency for Medicines.

The product information of the most popular OTC vaginal estriol in Finland (Ovestin®) lists estrogen dependent tumors as contraindication, mentions tender breasts (mastodynia) as an adverse reaction, advises patients with long-term estrogen treatment to have regular physician check-ups and recommends regular physician surveillance for women with a wide variety of diseases (most of which women themselves cannot diagnose).

As a part of a larger study on physicians' opinions on self-medication, the purpose of this study was to find out what Finnish physicians think about the fact that vaginal estriol does not require a prescription, and if they have found any problems resulting from self-treatment with these drugs.

2. Methods

This study was based on a questionnaire survey on OTC-drugs sent to gynecologists and specialists in general practice (GP) in Finland in 1996. A consecutive sample of working-aged physicians in six out of 12 counties in Finland was picked from the register of health professionals. This register is kept by National Research and Development Center for Welfare and Health and covers all licensed physicians. For the sample every second physician from a name list arranged by postal zip codes was picked. Out of the 457 physicians, 341 (75%; 77% excluding uneligible respondents) answered; the response rate was equally good among gynecologists and GPs.

Table 1
Physicians' characterisation

	Gynecologist ($n = 126$)	GP ($n = 215$)	Total ($n = 341$)
Mean age (S.D.)	47.4 (7.8)	46.5 (6.4)	46.8 (6.9)
Mean graduation year (S.D.)	75.1 (6.9)	75.9 (5.7)	75.6 (6.2)
Women (%)	51	48	49
Works[a]			
In hospital (%)	62	11	30
Health centre (%)	4	59	38
Private practice (%)	26	4	12
Other (%)	8	27	20[b]
Prescribet HT[c], last 6 months (%)	98	72	82[b]

[a] Main employment.
[b] The difference between gynecologists and GPs is statistically significant, $P < 0.001$ (for the distribution in the case of the workplace).
[c] HT, hormone therapy for menopause or postmenopause.

One of the questions was 'In the 1990s Ovestin® vaginal suppositories and cream and Pausanol® cream were given OTC status. Has this change to OTC status in your mind been a good thing? (You may choose more than one option); (1) Yes, why? (2) No, why? (3) Cannot say'. Both Ovestin® and Pausand® contain estriol. Another question was 'Have you observed in your work any problems related to the OTC use of estrogen drugs? (1) No (2) Yes, please specify. 'Because all OTC estrogen drugs in Finland contain estriol, this term is used when the results of this question are presented. Ovestin® suppositories was one of the products in lists of drugs given in two general questions: 'What do you think of the suitability of the following drugs for OTC status?' With options: 'well suited, somewhat suited, not suited, cannot say' and 'Who in your mind is the best provider of drug information regarding the following drugs?' with options 'a physician, pharmacy personnel, literature (patient leaflets) is enough, no difference, cannot say'.

The statistical significance of the differences between the groups was tested using the test of two proportions and t-tests.

Table 1 describes the background characteristics of the study physicians. The prescription of menopausal and postmenopausal hormones in the past 1/2-year was used as a proxy indicator for seeing middle-aged and older women, the target group for vaginal estriol. Practically all gynecologists and most GPs had had such patients.

3. Results

When asked in a structured question whether giving estriol-containing vaginal creams (specifying the trade-names) OTC-status in the 1990s was a good thing, most physicians said 'yes', (Table 2). Only 12% thought it to be a negative development, and the rest did not have a clear opinion or said that OTC status was both positive and negative. There was no big difference in regard to physicians' gender, age or graduation year. But gynecologists more often than GPs held positive opinions (Table 2), and GPs more often did not have a clear opinion. Gynecologists in private practice more often expressed a negative opinion (24%) than did hospital gynecologists (6%, $P < 0.05$), who more often were less sure of their opinion. Physicians who had not prescribed menopausal or postmenopausal therapy during the past 6 months were much more likely to choose the 'cannot say' alternative than physicians who had prescribed these drugs.

Physicians considered vaginal estriol to be somewhat less suitable for self-care than local drugs against vaginal candida, but they were much more negative about self-care with contraceptive pills and about emergency contraception with hormone pills (Table 2). Vaginal candida drugs are currently OTC drugs in Finland, but the two last mentioned are not.

When asked in an open question for reasons for their opinion, 77% of the physicians who considered the switch of estriol creams to OTC status to be positive, gave one or more reasons. The most common reason (54% of respondents) referred to increased access, such as it being easier, quicker or cheaper for patients. Other reasons referred to the safety and efficacy of the drug (29%) and the importance of self-care (13%). Only 8% explicitly said that OTC drugs make physicians' work easier and 2% that it reduces the costs for society.

Of the 64 physicians considering the switch of estriol creams to OTC status to be negative, 95% gave reasons for their opinion. By far the most common reason was related to the general dangers of self-care: 62% referred to postponement of care seeking and correct diagnosis, and to a reduction in seeking health check ups. In addition, 26% gave explanations relating to competence and quackery or referred to information and other problems in self-care. Only 23% gave drug effects (adverse effects or ineffectiveness) as a reason for their negative opinion.

When given a list of 12 trade names and asked to estimate each product's suitability for self-care, physicians considered estriol creams to be equally suitable for self-care as most of the other example drugs in the list recently given to OTC status. Instead, drugs which at the time of the survey still required a prescription or were transferred during the survey for OTC use were much more rarely judged to be suitable for self-care.

When physicians were asked in a structured question about whether they had seen in their work any problems relating to self-care with estriol creams, 12% said 'yes' (Table 3); 79% said 'no' and the rest were not doing clinical work or the question was not answered. Gynecologists were much more likely to report having seen problems. This was especially true of gynecologists in private practice. Of the 33 private gynecologists 49% reported having observed problems. Those GPs ($n = 53$) who had frequently prescribed (post)menopausal hormones in the past $\frac{1}{2}$ year, i.e. had seen mid-aged women, more often (13%) than other GPs reported having observed some problems caused by OTC estriol (2%, $P < 0.01$). Physicians having a negative opinion of the OTC status of estriol creams more often (38%) had observed some problems than physicians who had a positive opinion (7%, $P < 0.001$). The differences by other background characteristics were small.

The types of problems observed, asked about in an open question and coded later, were similar to the reasons given for negative opinions on OTC switch. Most physicians reported self-care problems such as late care seeking (Table 3). But some gynecologists mentioned adverse effects of the drug itself, including endometrial hyperplasia and bleeding.

When asked in a structured question who is the best provider of drug information about vaginal estriol, specifying a trade-name (Ovestin® vaginal suppositories), about equal numbers chose physicians and pharmacy personnel, and 16% thought written information to be enough, Table 4. (A few physicians had chosen both 'physician and pharmacy personnel' or 'pharmacy personnel and written information': these were coded into the last

Table 2
Proportion of physicians considering some gynecological drugs to be suitable for OTC status[a] (%)

	Gynecologists ($n = 126$)	GP ($n = 215$)	Total ($n = 341$)
Vaginal estriol	69	54	60[b]
Vaginal candida drugs	73	78	76
Contraceptive pill	6	5	5
Emergency contraception	24	23	23

[a] The two first mentioned are OTC drugs ('Was the change a good thing?'), the two last mentioned are not ('Should they be given OTC status?').

[b] The difference between gynecologists and GPs is statistically significant, $P < 0.001$.

Table 3
Proportions of physicians having observed problems related to the OTC status of vaginal estriol[a] (%)

	Gynecologists ($n = 126$)	GP ($n = 215$)	Total ($n = 341$)
Some problem	24	5	12[d]
Late care-seeking	11	4	7[b]
Ineffective usage patterns, underuse	5	1	2
Wrong indications, overuse	6	<1	2[c]
Pharmacological			
Endometrial hyperplasis, bleeding	5	0	2[c]
Allergy	2	0	1
Breast tenderness	1	0	<1

[a] Each physician could have listed more than one problem.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.001$, the difference between gynecologists and GPs is statistically significant.

mentioned options.) Gynecologists less often than GPs cited pharmacy personnel (30 vs. 43%, $P < 0.05$), and more often chose a physician or written information. A physician was considered the best information provider for estriol more often than for most other OTC drugs, for which pharmacy personnel were more often chosen. Table 4 gives as an example the distributions of responses concerning three typical drugs.

4. Discussion

Finnish physicians considered vaginal estriol to be suitable for OTC status, and to be much more suitable than the other estrogen-containing drugs asked about in our study: oral contraceptives and emergency contraception pills. On the other hand, many of them thought that the best information provider for vaginal estriol is a physician. An explanation for this contradiction in the opinions on OTC status and self-care may be physicians' general favorable attitude towards post-menopausal estrogen therapy [1]. Having an OTC drug provides easy access to the therapy and this may increase the use of estrogens, which many physicians would like to see. The importance of easy access was evident also in the reasons physicians gave for their support of the OTC status of vaginal estriol.

Another reason for the physicians' favorable opinions of the OTC status of vaginal estriol can be physicians' general trust in the drug licensing authority: drugs which already were OTC were assumed to be so for a reason. This explanation is supported by physicians' opinions about other drugs: if a drug already was OTC, it was much more frequently considered to be suitable for this status than drug(s) which were released OTC during or after the survey [17]. The pharmacological properties, safety or ease of self-diagnosis do not explain how physicians came to the conclusion that a drug is suitable for OTC status.

Gynecologists who worked in private practice and who thus were likely to see many post-menopausal women were more critical towards the OTC status of vaginal estriol, and also more frequently reported having seen adverse effects. However, most of the given adverse effects related to observed or potential delays in care seeking. Potentially, self-care decreases the need for professional visits. But it is impossible to untangle in our survey whether the reason for their critical attitude was a realistic picture of the suitability of vaginal estriol for self-care or was the need to have patients.

Vaginal irritation (burning and itching), which is the most commonly reported adverse effect in the literature [2,4,10], was not reported by our study physicians. This may be due to the fact that we asked about problems related to self-care, and physicians may have considered local reactions to be unrelated to self-care or to be so self-evident and banal that they were not worth reporting.

Additionally, physicians' observations of adverse effects without a systematic data collection and control groups, are not vey useful in assessing the frequencies of adverse effects. Physicians' reports of allergic reactions and breast tenderness were in accordance with results of some clinical trials [2,16]. But because the trials did not contain a placebo group, the causality between estriol use and these symptoms cannot be determined from the trials either.

From the survey results, a picture of physicians' ideal pattern of vaginal estriol use can be constructed: A woman discusses the need for vaginal estriol with her own physician, attends check-ups regularly, but buys the drug on her own initiative from a pharmacy. In this ideal situation less paperwork is needed and money is saved because visits just to refill a prescription and the prescription of too large quantities at one time resulting in unused drugs is avoided. The patient does not pay much more, because in the Finnish drug reimbursement system the proportion paid by the patient herself is high for low prize products. Unfortunately we do not know how well this ideal occurs, because we have no data on women's actual behavior, or how often vaginal estrogen drugs are bought by a physician's recommendation.

Most Finnish physicians in this survey were happy with the OTC-status of vaginal estriol products. But is vaginal estriol suitable for self-care without any physician contact? Much of the discussion this far has concerned endometrial hyperplasia as a risk factor for cancer. Reports this far have been reassuring, but no large-scale epidemiological studies on long-term use of vaginal estriol or other estrogens exist. In the United States conjugated estrogens rather than estriol are commonly used in vaginal preparations. There the American College of Obstetricians and Gynecologists has recommended concomitant progestin therapy for women receiving vaginal estrogen [18]. Such a requirement makes self-care with vaginal estrogens impossible—unless progestins are made OTC drugs, too. In Finland, progestins are not recommended to be used with local estriol treatments. If we assume that women taking vaginal estriol long-term contact physicians regularily, then also other topical postmenopausal estrogen or estrogen-progestin therapy—when advised to be taken in low dosages and contacting physicians regularily—could be available without prescription.

The sales figures showed that in Finland vaginal estrogens are commonly used and their popularity is increasing. In 1996 in Finland, 7.0 defined daily doses (DDD) of vaginal estrogens per 1000 inhabitants were sold, most of which were available without prescription. In the same year, the total sales of estrogens commonly used for menopause and postmenopause was 40.4 DDD [7]. The market is large because many postmenopausal women complain of urogenital symptoms [8]. Literature on possible biological adverse effects calls for studies on the safety of long-term use of vaginal estrogens, including estriol. And the study physicians' worry about delayed care-seeking call for studies on usage patterns. In studies of menopausal and postmenopausal hormone therapy, the use of vaginal estrogens should be specifically inquired about and its relation to other hormone therapy and health outcomes, including possible adverse effects, studied. Meanwhile, patient leaflets and other user information

Table 4
Physicians' opinions of the best provider of drug information for vaginal estriols, as compared to some other OTC drugs (%) ($n = 341$)

	Physician	Pharmacists	Written information	Other[a]	Total
Estriol 0.5 mg vaginal suppositories (Ovestin®)	39	37	16	8	100
Mikonatsol 400 mg vaginal cream (Gyno-Daktarin®)	22	49	24	5	100
Acyclovir 5% ointment (Zovirax®)	28	49	19	4	100
Sucralfate 1 g tablets (Alsucral®)	21	49	18	12	100

[a] No difference, cannot say, no information.

of vaginal estrogens should be more specific on how the contraindications and adverse effects currently listed can be observed. Patient information could include a statement that the therapy should not be used without an intitial physician check-up and that later visits for drug-effect surveillance are recommended. On the other hand, the usefulness of having an OTC drug, for which physician surveillance is recommended, can be questioned.

References

[1] Hemminki E, Topo P. Prescribing of hormone therapy in menopause. J Psychosom Obstet Gynecol 1997;18:145–57.

[2] Barentsen R, van de Weijer PH, Schram JH. Continuous low dose estradiol released from a vaginal ring versus estriol vaginal cream for urogenital atrophy. Eur J Obstet Gynecol Reprod Biol 1997;71:73–80.

[3] Bottiglione F, Volpe A, Esposito G, Aloysio DD. Transvaginal estriol administration in postmenopausal women: a double blind comparative study of two different doses. Maturitas 1995;22:227–32.

[4] Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. New Engl J Med 1993;329:753–6.

[5] Nordic Council on Medicines. Nordic Statistics on Medicines 1993–1995. NLN Publication No 43. Uppsala 1996: 45–7.

[6] Fallsberg M, Holme Hansen E. Håndkøpsmedicin-danske og europaeiske perspektiver. Sundhedsstyrelsen, København 1995: 28–9.

[7] National Agency for Medicines and Kela. Finnish Statistics on Medicines 1996. Helsinki 1997; 170–2.

[8] Nilsson K, Heimer G, Risberg B, Hanson U. Cytohormonal analysis of urogenital estrogen deficiency. A study on the impact on vaginal atrophy of various coexisting factors and the prevalence of urogenital symptoms and estrogen treatment. In: Nilsson K. Urogenital oestrogen deficiecy in the postmenopause. Uppsala Dissertations, Faculty of Medicine 498, Acta Universitatis Upsaliensis, Uppsala 1994.

[9] Martin PL, Yen SSC, Burnier AM, Hermann H. Systemic absorption and sustained effects of vaginal oestrogen creams. J Am Med Assoc 1979;242:2699–700.

[10] Iosif CS. Effects of protracted administration of estriol on the lower genitourinary tract in postmenopausal women. Arch Gynecol Obstet 1992;251:115–20.

[11] Calaf Alsina J. Perception and use of local hormone replacement therapy. Eur Menopause J 1996;3:85–9.

[12] van Haaften M, Donker GH, Sie-Go DM, Haspels AA, Thijssen JH. Biochemical and histological effects of vaginal estriol and estradiol applications on the endometrium, myometrium and vagina of postmenopausal women. Gynecol Endocrinol 1997;11:175–85.

[13] Melis GB, Cagnacci A, Bruni V, et al. Salmon calcitonin plus intravaginal estriol: an effective treatment for the menopause. Maturitas 1996;24:83–90.

[14] Vooijs GP, Geurts TB. Review of the endometrial safety during intravaginal treatment with estriol. Eur J Obstet Gynecol Reprod Biol 1995;62:101–6.

[15] Montoneri C, Zarbo G, Garofalo A, Giardinella S. Effects of estriol administration on human postmenopausal endometrium. Clin Exp Obst Gyn 1987;14:178–81.

[16] Henriksson L, Stjernquist M, Boquist L, Ålander U, Selinus I. A comparative multicentre study of the effects of continuous low-dose estradiol released from a new vaginal ring versus estriol vaginal pessaries in postmenopausal women with symptoms and signs of urogenital atrophy. Am J Obstet Gynecol 1994;171:624–32.

[17] Sihvo S, Hemminki E, Ahonen R. Physicians' attitudes toward reclassifying drugs as over-the-counter. Med Care 1999, in press.

[18] Handa VL, Bachus KE, Johnston WW, Robboy SJ, Hammond CB. Vaginal administration of low-dose conjugated oestrogens: systemic absorption and effects on the endometrium. Obstet Gynecol 1994;84:215–8.