ELSEVIER

Maturitas 42 (2002) 149–156

MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL

www.elsevier.com/locate/maturitas

The effects of oral estriol on the endometrium in postmenopausal women

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Received 5 March 2001; received in revised form 10 February 2002; accepted 28 February 2002

Abstract

Objectives: To study the long-term effects of oral estriol tablets on the endometrium of postmenopausal women by TVS and histology. *Method:* This was a cross sectional, parallel-group, multicenter trial of 241 postmenopausal women, out of whom 125 were treated with oral estriol and 116 were untreated controls. Endometrial histology using Pipelle biopsies and/or dilatation and curettage (D&C) was taken, endometrial thickness was assessed by use of transvaginal ultrasound (TVS), and the relation between endometrial thickness and histology was calculated. *Results*: No statistically significant differences between the two groups were found in endometrial histology. There were found more polyps in the oral estriol group (14.0%) as compared with the control group (2.9%). The mean endometrial thickness in the oral estriol group was 3.0 mm compared with a mean value of 2.4 mm in the control group: $P = 0.01$. *Conclusions:* No clinically relevant difference was found between the endometrium status (assessed by histology and TVS) of postmenopausal women on long-term oral estriol therapy and untreated controls. This trial supports the endometrial safety of maintenance treatment with oral estriol tablets. However, there are signs, not statistically significant, that may be associated with more endometrial polyps in postmenopausal women than if therapy is not given and that TVS is a useful instrument for the diagnosis.

Keywords: Estriol; Ultrasound; Postmenopausal women; Endometrium

1. Introduction

Oral estriol tablets have been used with good effects, primarily for the treatment of local urogenital complaints in postmenopausal women for over 40 years [1]. One of its product characteristics is that it does not stimulate the endometrium and can, therefore, be used uninterrupted, without the cyclical addition of a progestogen to protect the endometrium. Although all available data confirm the endometrial safety of oral estriol tablets, it was found relevant to update the existing long-term data on this topic.

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0378-5122/02/$ - see front matter
PII: S0378-5122(02)00037-3

Sonographic imaging of the endometrium has been improved by the development and several studies have been published where transvaginal sonography (TVS) was performed in women with postmenopausal bleeding (PMB) and the thickness of the endometrium measured by TVS was correlated to the histopathological diagnosis [2–9]. In the 'Nordic trial' presented by Karlsson et al. no endometrial cancer was found in women with PMB who had an endometrial thickness ≤ 4 mm [4]. If this cut-off had been used for performing an endometrial biopsy, 46% of the dilatation and curettage (D&C) operations would not have been necessary [4]. The results from the Nordic study have been reproduced in an Italian multicenter trial, by Ferrazzi et al. [5].

Despite TVS allows accurate measurement of the endometrium thickness and has proved to have a high detection rate and low false positive rate for diagnosis of endometrial pathology in postmenopausal women, for many regulatory authorities the safety of estrogen treatment on the endometrium remains to be proven by endometrium histology rather than by TVS [11]. Therefore, the primary parameter of this trial is the histological diagnosis based on the results of Pipelle biopsies or on abrasio. The combination of Pipelle biopsies and TVS has been shown to provide highly accurate information on the endometrium in postmenopausal women [12].

The trial was conducted in compliance with the declaration of Helsinki and its most current revisions, Good Clinical Practice (GCP) standards and the National Regulations in Sweden where the trial was conducted.

The Ethics Committee of each center approved the trial. Each subject gave written informed consent before starting any trial-related activity.

2. Aim of the study

To provide data on the long-term effects of oral estriol tablets on the endometrium of postmenopausal women by vaginal ultrasonographic examination and endometrial biopsies (histology). In addition, the correlation between the endometrial biopsy results and the results of ultrasonographic examination of the endometrium was investigated.

3. Statistical methods

Univariate comparisons of the sample distributions for continuous variables (age, endocrinology and maturation index) between the Oral estriol group and the control group were done by the standard two-sample (Student's) t-test (tested two-sided at a significance level of 5%.

All statistical procedures (listings, analysis) were performed with SAS version 6.11 on the AIX (IBM-UNIX) operating system.

4. Material and methods

The women were recruited in two hospitals (Gothenburg and Hudiksvall, both in Sweden) via an open procedure (advertisement).

The trial was performed from October 1994 to March 1995. The trial was designed as an open comparative two-center cross-sectional investigation.

TVS and histology of the endometrium were to be assessed in 125 postmenopausal women who had been treated with either 1 or 2 mg oral estriol tablets. The results of this group were compared with those of a control group of 116 postmenopausal women who had not received any hormone replacement therapy for at least 1 year (hereafter called the control group).

Women who met any of the following general or group-specific criteria were excluded from the trial: Hysterectomy and bilateral oophorectomy. In oral estriol group the use of any other HRT than oral estriol tablets in the past year and in the control group: the use of any HRT in the past year.

Flow assessments of patients was as follows: medical/gynecological history, physical examination, gynecological examination, Papanicolau cervical smear, TVS, Pipelle endometrial biopsy, blood sampling (sampling was used for determination of E2, E3 and FSH levels in plasma).

In the group of women who had used oral estriol in the past year, compliance to treatment was checked by means of inquiry by the investigator and by the karyopycnotic index (KPI) of the vaginal mucosa. In the control group, the 'non-use' of hormone replacement therapy was checked by means of estriol and estradiol plasma levels and by KPI of the vaginal mucosa.

All the women underwent a gynecological examination and a TVS examination using high frequency (5–7.5 MHz) transducers from different manufacturers. The uterus was scanned longitudinally and transversely. All women had voided bladders and were scanned in the lithotomy position with a slight reverse Trendelenburg tilt to localize free fluid in the pouch of Douglas. Endometrial thickness was measured in the longitudinal plane. The measurement included both endometrial layers; i.e. the measurement was performed between the two basal layers of the anterior and posterior uterine wall at the thickest point. To evaluate the whole endometrium, the cavity was examined sagittally from cornu to cornu to get the best measuring plane and not to miss any focal abnormality. The adnexal region was also covered with TVS to exclude extrauterine pelvic masses. Only gynecologists very experienced in transvaginal ultrasound performed the scans.

Preferably before performing TVS, a vaginal smear was to be taken.

Pipelle endometrial biopsies and, if applicable, also D&C were used to assess endometrial histology. The Pipelle method of endometrium biopsy sampling causes less discomfort and is safer than traditional D&C, while maintaining diagnostic accuracy [12]. Its methodology and results have generally been accepted. The endometrial evaluations were performed by two independent pathologists who had to classify each slide according to categories as specified in the protocol. However, since these pathologists did not use uniform guidelines for classification of the endometrial slides, a third pathologist with specific expertise on the evaluation of hormonal effects on the histology of the endometrium was consulted to make the final evaluation of the endometrial slides. The histological diagnosis of the endometrium was categorized according to Dr C. Bergeron (laboratoire cerba, Cergy Pontoise, France) [13]. If pathology was suspected based on either the result of a Pipelle biopsy or on endometrial thickness measured by TVS, also an abrasio was performed. If for one subject both a biopsy and abrasio result was achieved, the abrasio result was regarded as the final outcome. The primary parameter to be analyzed is the histological diagnosis either based on the biopsy result or on abrasio. Simple, descriptive statistical tables were used to present for both groups the frequency of the histological diagnoses used at the endometrial evaluation.

Plasma hormone levels were determined to check the postmenopausal status (follicle-stimulating hormone levels) and, together with the KPI, to check the 'non-use' of hormone replacement therapy (estradiol and estriol levels). Furthermore, since age and estriol level may influence the endometrial status, summary statistics for each of these two variables were given for each histological diagnosis, separately for both groups.

The secondary analysis evaluated the interdependency between the result of the endometrial thickness (as assessed by TVS) and the endometrial histology diagnosis. This interdependency is illustrated by presenting for each diagnosis category summary statistics for the endometrium thickness, separately for both groups.

5. Results

Data from 241 (242 minus 1, one woman did not fulfill the inclusion criterion on body weight and was excluded) women were included in the analysis, 125 with an mean age of 64.2 (S.D. 5.8, range 55–76 years) in the oral estriol group and 116 with an mean age of 66.4 (S.D. 6.2, range 55–79 years) in the control group.

The number of women with clinically significant pre-existing conditions in their medical history (e.g. conditions which required hospitalization or chronic conditions requiring treatment) are given in Table 1.

In the oral estriol group, the subjects took either 1 or 2 mg tablets (mean 1.55 mg) and the

mean treatment duration was 4.3 years (median 3 years) in this group. The drug was prescribed for vaginal symptoms in 90 women (72%) and/or, urinary symptoms in 60 women (48%) and/or for other indications in three women (3%). In the control group also, there were 14 women with a history of oral estriol treatment in dosages ranging from 0.5 to 2 mg/day during 0.5–15 years, but this treatment had been stopped at least 1 year before the trial entry.

An histological diagnosis was obtained for 201 women. In 40 cases no endometrial evaluation could be made due to anatomical conditions such as cervical stenosis, narrow vagina and not visible portio due to atrophy. Table 2 presents an overview of the histological diagnosis based on either the result of a Pipelle biopsy or on abrasio for each trial group. Of the 201 histological diagnoses, 99 were made in the oral estriol group and 102 in the control group. In the oral estriol group, 14 diagnoses were made based on the D&C results and the remaining 85 were based on the result of the Pipelle biopsy. For the control group these figures were three D&C and 99 biopsy diagnoses.

Table 1
Number of women with pre-existing clinical conditions

	Oral estriol group ($n = 125$)	Control group ($n = 116$)
Sensory organs	0	2
Nervous system	2	2
Cardiovascular system	15	15
Respiratory system	3	4
Gastrointestinal tract	7	3
Liver	0	1
Endocrine system	4	6
Urogenital system	12	5
Musculoskeletal system	6	3
Allergic conditions	0	0
Hematological conditions	1	0
Skin	0	1
Other	2	0

Table 2
Number of women with a histological diagnosis per trial group

Category-description	Oral estriol group	Control group
No tissue obtained	2	0
Tissue insufficient for diagnosis	18	20
Atrophic and/or inactive endometrium	63	77
Secretory endometrium	0	0
Menstrual type endometrium	0	0
Proliferative endometrium	0	0
Polyps	14	3
Hyperplastic endometrium	0	0
Carcinomaendometrioid type	0	1
Other (e.g. inflammation)	2	1
Total	99	102

As shown in Table 2, most of the endometrial slides were diagnosed as atrophic, but one endometrial carcinoma was found in the control group. There was found 14.1% (14/99) polyps in the oral estriol group. The corresponding figure for the control group was 2.9% (3/102). However, the histopathological diagnosis between the groups are not statistically significant.

The mean endometrial thickness, in women with atrophic endometrium, in the oral estriol group was 3.0 mm (S.D. 1.8) compared with a mean value of 2.4 mm (S.D. 1.4) in the control group (two-sided ($= 0.05$) t-test: $P = 0.01$). The corresponding figures for women with insufficient tissue obtained at biopsy and polyps are shown in Table 3. The mean endometrial thickness in all women included in the oral estriol group was 3.7 mm (S.D. $= 2.83$, range 1–19 mm). The corresponding figures for the control group was 2.5 (S.D. $= 1.75$, range 1–11 mm). In the oral estriol group 89% had an endometrium measuring ≤ 4 mm, 10% 5–7 mm and 1% ≥ 8 mm. The corresponding figures for the control group were 97, 3 and 0% Table 3.

The TVS measurement of the uterus did not show any statistical different values concerning the uterine length, width and height between the groups.

A vaginal smear for determination of the KPI could be obtained for 140 women. For 51 women (44%) in the control group and 50 women (40%) in the oral estriol group no vaginal smear results were obtained due to fixation problems (control group, $n = 34$; oral estriol group, $n = 24$), impossibility of obtaining a vaginal smear (control, $n = 5$; oral estriol, $n = 11$), low maturation or atrophy (control, $n = 7$; oral estriol, $n = 14$), inflammation (control, $n = 4$; oral estriol, $n = 1$) and errors (oral estriol, $n = 1$).

The KPI and the MI figures were statistically significantly higher in the oral estriol group compared with the control group. KPI in oral estriol group was 5.1 ± 10.7 and in control group 0.7 ± 2.8, $P = 0.0015$. The corresponding figures for MI were 33.6 ± 23.3 and 19.9 ± 20.8, 0.0004. Both these results reflect a more atrophic (i.e. less mature) state of the mean vaginal epithelium of the women in the control group compared with the state in the oral estriol group.

Table 3
Summary statistics for endometrial thickness, for each histological diagnosis

	Oral estriol group ($N = 99$) mean ± S.D.	Control group ($N = 102$) mean ± S.D.
No tissue obtained	3.5 ± 0.7 mm	–
Insufficient tissue	3.0 ± 1.6 mm	2.4 ± 1.7 mm
Atrophic/inactive endometrium	3.0 ± 1.8 mm	2.4 ± 1.4 mm
Secretory endometrium	–	–
Menstrual type endometrium	–	–
Proliferative endometrium	–	–
Polyps	8.9 ± 4.4 mm	5.7 ± 4.0 mm
Hyperplastic endometrium	–	–
Carcinoma-endometrioid type	–	11 mm
Other (e.g. inflammation)	3.5 ± 2.1 mm	2.0 mm

Table 4
Summary statistics for age and estriol, separately for each histological diagnosis

	Oral estriol group mean ± S.D.	Control group mean ± S.D.
Age (years)		
No tissue obtained	59.0 ± 5.7	–
Insufficient tissue	65.3 ± 6.3	66.7 ± 5.8
Atrophic/inactive endometrium	65.4 ± 6.0	63.3 ± 5.9
Polyps	69.8 ± 5.2	66.7 ± 4.0
Carcinoma-endometrioid type	–	62
Other (e.g. inflammation)	69.0 ± 1.4	61
Estriol (mmol/l)		
No tissue	65.0 ± 32.6	–
Insufficient tissue	45.4 ± 30.0	18.4 ± 2.8
Atrophic endometrium	52.8 ± 30.0	20.7 ± 7.8
Polyps	47.9 ± 30.0	<17
Carcinoma-endometrioid type	–	<17
Other (e.g. inflammation)	25.0 ± 11.3	25

There was found no statistically significant difference in mean FSH levels between the two treatment groups. In the oral estriol group FSH was found to be prior to the study 74.1 S.D. 24.0. The corresponding figures for the control group was 78.9 and 24.1, $P = 012$.

The distributions of age and estriol are different between the oral estriol group and control group. However, since relevant differences were found between the histological diagnosis in both groups, no relationship could be established between either age or estriol plasma level and histological diagnosis (Table 4).

No adverse events were reported in this (cross-sectional) trial. Laboratory parameters were not applicable. The general medical examinations did not reveal any abnormalities. No clinically relevant differences in gynecological history between the two groups were observed, concerning age at menopause, pregnancies or parity.

The vital signs parameters blood pressure, heart rate, body weight and height observed did not differ between the two groups.

Nine of the 125 women (7%) in the Oral estriol group and 11 of the 116 women (9%) in the control group smoked 4–20 cigarettes per day during 5–45 years. Fifteen women in the oral estriol group and 18 women in the control group had stopped smoking 1–38 years ago.

6. Discussion

In this open multicenter, cross-sectional trial, endometrial histology and endometrial thickness by means of TVS were used to study the long-term effects of oral treatment with estriol on the endometrium in postmenopausal women. In addition, the interdependency of these techniques was investigated.

Gull and co-workers reported from a random sample ($n = 1000$) of the total population of women aged 45–80 years that women without HRT had a mean endometrial thickness of 3.0 ± 0.1 mm. The corresponding figures for women on medium-potent estrogens + progestogen and women with oral estriol only were 5.1 ± 0.3 mm and 3.6 ± 0.3 mm, respectively [10]. Of non-treated women 90% had an endometrium measuring ≤ 4 mm, 7% had an endometrium measuring 5–7 mm and 3% had an endometrium measuring ≥ 8 mm while the corresponding figures for women with oral estriol only were 86, 7 and 7% [10].

These results are in agreement with our presented study in which the mean endometrial thickness in the oral estriol group was 3.0 mm compared with a mean value of 2.4 mm in the control group. Though statistically significant, this difference is not clinically relevant since both values are within the range of endometrial thickness reported in the literature for non-treated postmenopausal women. Furthermore, the figures are in agreement with the study by Gull and co-workers [10] concerning the percentage of women in different endometrial thickness groups as we found that 89% in the oral estriol group had an endometrium measuring ≤ 4 mm, 10% when the endometrium measured 5–7 mm and 1% when the endometrium measured ≥ 8 mm. The corresponding figures for the control groups were 97, 3 and 0%. Furthermore, Gull and co-workers [10] found 3.2% of endometrial polyps in the oral estriol group as compared with our study in which we found 14% in the oral estriol group and 2.9% in the Control group. Due to the cross-sectional design of the trial (baseline data are lacking) no conclusions can be drawn on the clinical implications of this finding. Further larger prospective randomized studies are needed to further elucidate this.

Among older postmenopausal women, local symptoms due to atrophy of the vaginal and urethral epithelium may predominate [14], which also held true in this presented study. Although medium-potency estrogens, mainly estradiol and conjugated estrogen, clearly alleviate these symptoms [14,15], benefits may be achieved by the use of low-potency estrogen (oral estriol) formulations administered orally (estriol) or intravaginal (estriol or estradiol in very low doses) [16–19]. Therefore, prescription of such formulations is common in several countries, particularly in Europe.

Is treatment with oral estriol formulations based on good scientific evidence? An increased risk of endometrial cancer after use of the more potent estrogens is well established, although this increase in risk may be reduced or prevented by addition of progestogen [20]. By contrast, the risk of endometrial cancer among users of oral estriol formulations has never been adequately quantified in epidemiological studies, except for a recent publication by Weiderpass et al [21]. If, as is generally assumed [17–19,22,23] such compounds provide symptomatic relief without adverse endometrial effects, more widespread use might be justified.

In a study by Weiderpass and co-workers [21] it has been found that after multivariate adjustment, oral use of estriol 1–2 mg daily increased the relative risk of endometrial cancer and endometrial atypical hyperplasia: the odds ratios for at least 5 years of use compared with never use were 3.0 (95% CI 2.0–4.4) and 8.3 (4.0–17.4), respectively. The association was stronger for well-dif-

ferentiated cancers and those with no or limited invasion. The excess relative risk was lost rapidly after cessation of treatment. No associations were observed between vaginal application of low-potency estrogen formulations and relative risk of endometrial neoplasia [21]. They concluded that close surveillance of patients is recommended [21].

However, the data from other epidemiological studies on low-potency estrogen formulations and endometrial cancer are scarce. In a hospital-based case-control study in Finland, a 60% decrease in the relative risk of endometrial cancer was found among women who took estriol orally [22]. In a population-based prospective cohort study in Sweden, women prescribed oral estriol showed no overall increase in the risk of endometrial cancer [24]. However, in both these studies data on duration and frequency of intake were not available [22,24].

There is some evidence that oral estriol may have systemic effects. Englund and colleagues showed that more than 50% of postmenopausal women treated with oral estriol 6 mg daily for 3 months had menstrual bleeding after addition of a progestogen [25]. This has, however, not been shown in women with 1–2 mg with oral estriol daily.

Owing to its low affinity, estriol binds to the estrogen receptor in vitro for a shorter time than medium or high-potency estrogens do [26]. Estriol administered orally is conjugated efficiently in the liver, but because estriol does not bind strongly to proteins, most of the serum estriol is biologically active [27,28]. When estriol is taken continuously in high doses, the persistently high serum concentrations can lead to long-standing proliferation of endometrial cells [29].

In the presented study the estriol serum levels were substantially higher in the oral estriol group compared with the control group. These findings are in agreement with other studies [16,30]. However, in 72 women (71%) of the control group, the estriol value was below 17 mol/l (i.e. the minimum detection level). This was also the case in 22 women (21%) of the oral estriol group, but 13 of these women had a KPI in accordance with the women with higher plasma levels of estriol. This can be taken as a sign of good compliance in this group. There were no association between the histological findings and the plasma estriol levels in each group.

6.1. Concluding remarks

No clinically relevant difference was found between the endometrium status (assessed by histology and TVS) of postmenopausal women on long-term oral estriol therapy and untreated controls. This trial supports the endometrial safety of maintenance treatment with oral estriol. However, there are signs, not statistically, that oral estriol may be associated with more endometrial polyps in postmenopausal women than if therapy is not given and that TVS is a useful instrument for this diagnosis.

Acknowledgements

We want to thank J. Prohazka, Organon AB, Göteborg, Sweden and C. Meihizen, N.V. Organon, Oss, Holland. We also want to thank the pathologists helping us with this study: A.G. Hanselaar* and W. Rydh**, C. Bergeron***, Departments of Pathology, *University of Nijmegen, Nijmegen, The Netherlands, **Sahlgrenska University Hospital, Gothenburg, Sweden and ***Laboratorie Pasteur-Cerba, Cergy Pontole Cedex, France.

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