



Review of the endometrial safety during intravaginal treatment with estriol

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Abstract

To gain more insight into whether intravaginal treatment of local urogenital complaints with the mild-acting oestrogen estriol is capable of inducing proliferation of the endometrium, the results of the clinical studies that have been published over the years have been pooled. Of a total of 19 studies that initially had been selected, four were excluded from the analysis because no baseline biopsies were available, two because endometriae had been evaluated using methods other than with histology, and one study because a sustained-release preparation was used. Pooling of 12 studies (214 subjects) revealed a reasonable amount of long-term data on intravaginal estriol treatment with 61 evaluable biopsies after 6 months and 58 after 12 months. In addition, 13 biopsies were available after 2 years. It appeared that intravaginal estriol treatment using the recommended dosages did not result in endometrial proliferation. All 337 post-baseline biopsies that have been reported in the literature were classified as atrophic. It can be concluded that single daily treatment with intravaginal estriol in the recommended doses in postmenopausal women is safe and without an increased risk of endometrial proliferation or hyperplasia. Consequently, there is no need to add sequential progestogens with these preparations and no withdrawal bleedings will be induced.

Keywords: Intravaginal estriol; Endometrial proliferation; Progestogens

1. Introduction

During the reproductive years, the three endogenous estrogens of importance are 17β -estradiol, estrone and estriol. About 5 years before the menopause, the endogenous production of 17β -estradiol starts to decrease, and after the menopause this production ceases almost completely. Consequently, estrone and (to a lesser extent) estriol become the main circulating endogenous estrogens. This decrease in endogenous estrogen production may result in a number of climacteric symptoms, including irregular bleeding, hot flushes, atrophy-related urogenital symptoms, and an increased risk of both osteoporosis and cardiovascular disease.

Epidemiological data have indicated that about 50% of otherwise healthy women over 60 years have symp-

toms related to urogenital atrophy [1]. The clinical symptoms are vaginal dryness, dyspareunia, itching, miction complaints, recurrent vaginal infections and lower urinary tract infections. Since estriol induces normalization of the vaginal, cervical and urethral epithelium [2,3] and thus helps to restore the normal microflora and the physiological pH in the vagina [4–6] both intravaginal and systemic treatment with estriol increases the resistance of the vaginal epithelial cells to infection and inflammation [4–6] and decreases the incidence of urogenital complaints [2,5,6]. Consequently, the use of exogenous estriol (Ovestin[®], Colpogyn[®], Ortho-Gynest[®]) has now widely been accepted as the preferred medication in the treatment of atrophy of the lower urogenital tract.

Unopposed estrogen replacement therapy with 17β -estradiol and conjugated estrogens has been associated with an increased risk of endometrial hyperplasia which may lead to endometrial carcinoma [7,8]. In order to prevent this, progestogens need to be added. Progesto-

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gen administration induces a secretory transformation of the endometrium followed by a withdrawal bleeding [9]. However, sequential addition of progestogens has negative effects since it induces thus a recurrence of cyclical withdrawal bleedings which is not acceptable to most postmenopausal women and which has been identified as a major cause of non-compliance [10,11]. Furthermore, other progestogen regimens such as continuous addition of progestogens may lead to unexpected irregular bleeding [12], which may also contribute to non-compliance. Finally, some of the positive effects of estrogen use, such as an improvement of the plasma lipid profile, may be diminished or even reversed by progestogen addition [13,14].

In this context, it is relevant to investigate whether also treatment with a mild acting estrogen such as estriol can lead to endometrial hyperplasia and thus whether progestogen addition is needed with estriol treatment. Whereas with respect to 17β -estradiol and conjugated estrogens there is an abundance of clinical and epidemiological evidence that there is indeed a relationship with endometrial hyperplasia and carcinoma, with estriol treatment such a relationship has not been found, although the amount of epidemiological data is limited. As a result of its pharmacological profile, the risk of endometrial proliferation with estriol seems to be absent, since receptor binding studies have indicated that estriol has only low relative binding affinity to endometrial estrogen receptors (about 10% of 17β -estradiol), whereas it has a relatively strong binding affinity to vaginal estrogen receptors (equal to 17β -estradiol). This means that after a single dose of estriol, the binding to the endometrial estrogen receptor is too short to induce true proliferation, while its binding to the vaginal estrogen receptor is sufficient to exert a full vaginotropic effect [15]. This lack of endometrial proliferation has been supported by data from two epidemiological studies on estriol showing that there is no increased risk of endometrial carcinoma [16,17]. It can therefore be argued that with estriol treatment, when used in the recommended single daily dosages, the risk of endometrial hyperplasia is probably absent.

The objective of this review is to gain more insight in the effects of intravaginally administered estriol on the endometrium by pooling the results of the clinical studies that have been published over the years.

2. Methods

Literature from the period from the end of the 1950s (when estriol became available to the market) up to June 1994 was identified with help of detailed literature searches in commercial on-line databases (MedLine, Embase, Biosis, Current Contents) as well as with the help of in-house electronic literature databases and literature collections.

By checking the contents of the papers it was also attempted to exclude duplicate publications as far as possible, but since such papers often cannot be identified it may be possible that occasionally (parts of) duplicate data sets have been included. Studies evaluating the effects of oral preparations or intravaginal sustained-release preparations were also excluded from the analysis, since their pharmacokinetic and pharmacodynamic characteristics are thought to differ considerably from the intravaginal formulations. Finally, studies in which the endometrial biopsies were not evaluated by use of light microscopy were excluded from the analysis, since the typical definitions of atrophic, proliferative, secretory and hyperplastic endometria are based on the light-microscopical picture.

Requirements for inclusion were that from a particular study both baseline and follow-up biopsies should be available, since it is not uncommon for peri- and postmenopausal women to present with endometrium proliferation irrespective of estrogen use [9,18]. Absence of baseline biopsies makes it therefore impossible to determine causality with estriol use. Another requirement for a paper to be included was that the subjects should be postmenopausal. It was further decided to restrict this review to intravaginal administration, i.e. cream or suppositories, only in the recommended dosages (0.5 mg — one application, resp. one suppository — per day for the first 2–3 weeks, followed by a gradual reduction to 0.5 mg twice a week).

All studies that complied with the in- and exclusion criteria were evaluated with respect to the effects of estriol treatment on the endometrium. The evaluated and classified endometrial biopsies in the papers were tabulated and the proportion of biopsies that showed endometrial proliferation was subsequently analyzed. A complicating factor in analyzing endometrial histological data was that usually no exact definitions were presented for atrophy, proliferation, secretion and hyperplasia. However, in many light microscopy studies criteria similar to those below were used [18,19]:

— *atrophic endometrium*: this broad category includes the patterns of marked atrophy, inactive cystic endometrial atrophy of perimenopausal type, posthyperplastic atrophy and progestogen-suppressed endometrium. Some epithelial snouts and vacuoles may be present;

— *proliferative endometrium*: the endometrium shows discernible evidence of stimulation — the tissue is composed of single round or oval glands surrounded by a densely packed stroma. As a sign of active growth in both structures, numerous mitoses indicating cell division can be easily found;

— *hyperplastic endometrium*: a spectrum of glandular patterns, crowding (glands at the expense of stroma) and cytological abnormalities characterize the diagnostic

subcategories of cystic, adenomatous, and atypical hyperplasia. During persistent oestrogenic stimulation, glandular cystic hyperplasia may progress to adenomatous hyperplasia. Proliferating glandular epithelial cells cause a relative overgrowth of stroma cells and hyperestrogenism becomes manifest by the appearance of foam cells. Atypical hyperplasia is a more advanced stage and the glandular abnormalities are more closely related to those of adenocarcinoma. The lesion is characterised by large glands which lie closely together but are still separated by definite stroma strands. The glandular epithelial cells are frequently enlarged and pseudostratified. The glandular lining epithelium may show papillary folding. The cytoplasm is amphophilic or basophilic and the nuclei are enlarged and often differ in size. They may have a basal or intermediate position and show stratification and sometimes a slightly altered polarity. The nuclear chromatin is coarsely granular and unevenly distributed. Mitoses are common and the increased polymorphism of glandular cells is usually not evenly distributed within the glandular epithelium;

— *secretory endometrium*: glands may show subnuclear glycogen vacuoles with more advanced secretory change and glands are tortuous with luminal secretion. Stroma is hypertrophic with peri-arteriolar cuffing. Mitoses are rare or absent.

3. Results

A total of 19 possibly relevant studies were identified. Four studies were excluded from the analysis because from these, no baseline biopsies were available [20–23]. Three other papers were excluded because no biopsies had been taken and endometrium proliferation was evaluated otherwise, i.e. by induction of withdrawal bleeding with progestogens [24,25] or with the help of scanning electron microscopy (SEM) [26]. Finally, a study with a sustained-release estriol preparation was also excluded [27]. In three of the excluded papers signs of endometrial stimulation or other estrogenic effects have been reported [22,25,26]. In the electron microscopy study ciliogenesis with longer microvilli was observed in the estriol-treated group as compared to an untreated control group [26]. Although these effects can be explained as estrogenic in nature [28,29], it is unknown whether such estriol-induced effects as observed with SEM are synonymous with the light-microscopical phenomenon or with endometrial proliferation. Another limitation of this study was that no baseline assessments had been performed, leaving the possibility open that the effects were already present at baseline. In another excluded study where signs of endometrial stimulation were reported [22], no baseline biopsies had been taken and only indirect histological indices ('no influence', 'moderate influence', or 'full influence') were presented, making it impossible to determine a causal relationship

Table 1

Number of evaluable subjects per study at baseline and per treatment period (for all post-baseline biopsies an atrophic endometrium biopsy was present)

Reference	BL	2W	3W	1M	2M	3M	4M	6M	1Y	2Y
Babuna [30]	16	4	—	6	5	3	12	—	—	—
Boselli [31]	63	—	—	—	—	63	—	38	15	3
Boselli [32]	20	—	—	—	—	—	—	—	20	10
Genazzani [33]	12	12	12	—	—	—	—	—	—	—
Gerbardo [34]	23	—	—	—	—	—	—	23	23	—
Kicovic [35]	16	—	16	—	—	—	8	—	—	—
Lauritzen [36]	8	—	—	8	—	—	—	—	—	—
Luisi [37]	2	2	—	—	—	—	—	—	—	—
Mattsson [38]	6	6	—	—	—	—	—	—	—	—
Milojevic [39]	7	—	—	7	—	—	—	—	—	—
Trevoux [40]	15	—	15	—	—	—	—	—	—	—
van der Velden [41]	26	—	26	—	—	—	—	—	—	—
Total	214	24	69	21	5	66	20	61	58	13

with estriol. In the third study, in 7 out of 48 postmenopausal women there were signs of weak proliferation after 8–10 years of estriol treatment [25]. However, since no baseline biopsies were performed, the relationship with estriol is questionable.

Twelve studies were included in the analysis [30–41]. The total numbers of evaluable subjects per study at baseline (BL) and after 2 weeks (2W), 3 weeks (3W), 1 month (1M), 2 months (2M), 3 months (3M), 4 months (4M), 6 months (6M), 1 year (1YR) and 2 years (2YR) are presented in Table 1.

Table 1 indicates that pooling of the published data revealed a reasonable amount of long-term data on intravaginal estriol treatment with 61 resp. 58 evaluable biopsies after 6 and 12 months. In addition, 13 biopsies were available after 2 years of treatment.

From the results of the 12 studies mentioned in the table, encompassing a total of 214 subjects, it appears that intravaginal estriol treatment using the recommended dosages by postmenopausal women did not result in endometrial proliferation, not even after long-term (2 years) treatment. All 337 post-baseline biopsies were classified as atrophic by the authors of these papers. In addition, in the study by Lauritzen [36] even intravaginal treatment in a subgroup of subjects with 3 mg/day estriol for 1 week (not included in the tables), which is six times the recommended dose, did not induce endometrial proliferation.

4. Discussion

Estriol binds to the uterine estrogen receptor, forming a complex which ultimately accumulates in the cellular nucleus and attaches to specific binding sites. Of all the natural estrogens, estriol has the shortest receptor oc-

cupancy. The reasons for this are not clear but there are several possible explanations: a rapid dissociation from the estrogen receptor, a rapid plasma clearance and/or a rapid dissociation of complexes from nuclear binding sites. The critical binding period for stimulation of DNA synthesis and thus for endometrium proliferation lies between 9 and 12 h after first interaction, and when around this time point enough estrogen is bound to the receptor (e.g. after multiple daily doses or after high oral doses), stimulation of DNA synthesis will occur and a uterotrophic response may be seen [42–45]. As a result of the short duration of receptor binding of estriol following single daily doses, DNA synthesis is not stimulated and proliferation of the endometrium can therefore not occur. On the other hand, estriol exerts a full vaginotropic response. This differential effect on vaginal as compared to endometrial tissue may partly be explained by the presence of an estrogen-binding protein in the vagina which is not present in the endometrium. It has been demonstrated that estriol has a relatively high binding affinity to this vaginal protein [15].

Another consequence of the short duration of action of estriol at the receptor level is that there are hardly any systemic effects: studies indicate absence of effects on blood pressure [38], body weight [38], liver function [35], hemostasis [35,36], lipid metabolism [35,36] and bone metabolism [46]. With respect to effects of estriol on breast cancer risk, the available data give no reason for concern [47].

The decision to exclude studies from which no baseline biopsies were available is justified by the fact that at baseline endometrial proliferation may have been present: in a study in asymptomatic, predominantly white peri- and postmenopausal women it was reported that about 22% of endometrial biopsies showed proof of either proliferation or hyperplasia [18].

The results from studies with single daily intravaginal estriol treatment in postmenopausal women in the recommended dosages clearly and consistently demonstrate that endometrial proliferation does not occur. In addition, the findings in this review concur with the above mentioned mechanism of action studies in that with single daily intravaginal estriol treatment the binding to the endometrial estrogen receptor is too short to induce a proliferative effect. The findings are also in accordance with recent literature on the subject [5,48–50].

The limitations of the current findings are also clear: these results are only applicable to intravaginal estriol formulations and dosages mentioned in the 'Methods' section of this paper. No firm conclusions can be drawn with respect to oral preparations, intravaginal preparations using dosages higher than those recommended in this paper, multiple daily dosages or sustained-release preparations, because of differences in pharmacokinetic and/or pharmacodynamic characteristics. Nevertheless, available epidemiological studies indicate that with

estriol treatment in general there is no increased risk of endometrial cancer [16,17]. Another limitation of the current findings is that in the various studies, endometrial biopsies have been evaluated by different investigators who also may have used different standards and different subjects. However, since the results from all included studies show a non-response of the endometrium, they are probably generally applicable.

The main clinical implication of the lack of endometrial response is that with intravaginal estriol treatment, unlike treatment with longer-acting estrogens such as 17 β -estradiol or conjugated estrogens, no sequential progestogen addition is needed to prevent endometrial hyperplasia. Consequently, cyclical withdrawal bleeding will not be induced which has a positive effect on user compliance and a lack of potential progestogen-induced negative effects.

It can be concluded that single daily treatment with intravaginal estriol in the recommended doses in postmenopausal women is safe and without an increased risk of endometrial proliferation or hyperplasia. Consequently, there is no need to add sequential progestogens when using these preparations, not even for long-term treatment.

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