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Scanning Electron Microscopy of the Responses of Postmenopausal Endometrium to Treatment with Estriol and Estriolprogesterone

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ABSTRACT

Seven postmenopausal women were given estriol orally in a daily dose of 1 mg x 2 or 5 mg x 2 for 14 or 28 days and 2 women were sequentially treated with 5 mg x 2 of estriol orally for 21 days, with the addition of 0.2 g x 2 of progesterone rectally in the last 7 days. Three women served as controls. Scanning electron microscopy revealed that the former treatment with estriol was sufficient to produce an estrogen response in the non-ciliated uterine epithelial cells, which developed many long microvilli, sometimes arranged in tufts. The sequential treatment with initial estriol priming followed by estriol and progesterone combined resulted in a slight secretory transformation of the uterine epithelium, observed as an increase in size and number of the apical protrusions of the cells.

INTRODUCTION

Estriol in a dose of 1-4 mg per day is often given alone for the treatment of minor menopausal disorders, mainly dryness of the vagina, or in combination with estradiol as substitution therapy, often as part of a sequential course of treatment with gestagen. Even a small dose of estriol has a definite effect on the cervix and vagina (1,5,12), but this hormone has been considered to have no or only minimal influence on the endometrium (1,5,8,10,12), although estriol is known to bind to nuclei in this tissue (11). However, Heuser and Staemmler (6) and Englund and Johansson (4) have described both functional and light-microscopic changes of the endometrium following administration of estriol. Heuser and Staemmler (6) did not report whether the hormone was given as a single dose per day, but Englund and Johansson (4) gave three doses a day, thus coping with the problem of the short duration of an effective blood plasma concentration (3,4). The endometrial changes were found to appear after a period of 2-3 months.

Table I. *Data on patients and hormone schedules*

Case no.	Fig. no.	Years of age	Years of menopause	Types of hormone given	Day of biopsy (Day of artificial cycle)
Controls					
1	1	59	8		
2		60	8		
3		69	30		
Estriol treatment					
4		67	17	Estriol 2 mg.Days 1-14	15
5		59	7	Estriol 2 mg.Days 1-14	15
6		57	16	Estriol 2 mg.Days 1-28	29
7		59	20	Estriol 2 mg.Days 1-28	29
8		64	14	Estriol 10 mg.Days 1-14	15
9		57	3	Estriol 10 mg.Days 1-21	22
10	2	64	14	Estriol 10 mg.Days 1-21	22
Sequential treatment (estriol-progesterone)					
11		71	21	Estriol 10 mg.Days 1-21 Progesterone 0.4 g.Days 15-21	22
12	3	64	25	Estriol 10 mg.Days 1-21 Progesterone 0.4 g.Days 15-21	22

However, by applying a more sensitive indicator like scanning electron microscopy, it might be possible to demonstrate an endometrial effect even after a shorter period of treatment. The present study was therefore undertaken to ascertain whether short-term treatment with estriol alone would influence the endometrium, and whether this treatment would suffice for conditioning the mucosa for a gestagen response.

MATERIALS AND METHODS

Twelve postmenopausal women aged 57-71 years with prolapsed uterus were studied (Table I). The menopause had occurred 3-30 years prior to the trial. None of the patients had received estrogens or other steroids within the last two years. All patients were informed about the purpose of the trial, and all had given their verbal consent.

Therapy Groups

The control group consisted of 3 patients who received no treatment at all. Seven patients were given estriol (Ovestin^{R} 1 mg, Organon ApF, Copenhagen, Denmark) orally in a daily dose of 1 mg x 2 or 5 mg x 2 for 14 or 28 days. Two women were sequentially treated with 5 mg x 2 of estriol for 21 days, with the addition of 0.2 g x 2of progesterone, administered rectally, in the last 7 days (Table I).

Biopsies

All patients were to be operated on for prolapsed uterus. A biopsy was taken with a Reifferscheid curette from the anterior wall of the fundus in the midline, with the patient fully anesthetized. If possible two biopsies were taken, one for light microscopy and one for electron microscopy.

For scanning electron microscopy the specimens were washed for 30 sec in 0.1 M collidine buffer and fixed at pH 7.3 in 2.5% glutaraldehyde in the same buffer, rinsed in distilled water, dehydrated in acetone, and prepared by the critical point drying technique (9). The specimens were coated with gold-palladium and examined in a Jeol JSM-U3 scanning electron microscope.

RESULTS

Control group

The luminal surface of biopsies from the 3 women in the control group possessed slightly bulging cells, irregular in size, mostly with few, short microvilli (Fig. 1). Ciliated cells were sparse, but cells with a single kinocilium were often observed. This appearance of menopausal endometrium confirms previously observations (7, 9).

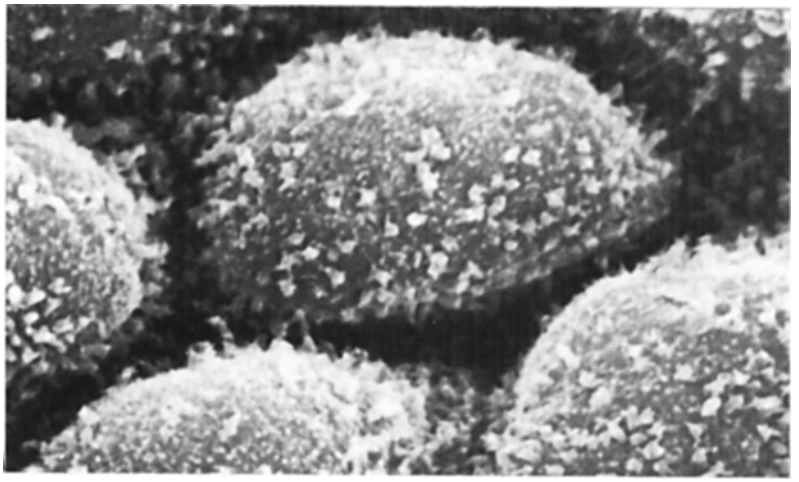

Fig. 1. Postmenopausal endometrial surface. Short microvilli are irregularly distributed on the cell surface (Case 1). X 11,000.

Estriol-treated group

Ciliated cells occurred frequently. The non-ciliated cells were bulging and displayed a fairly uniform surface area. The cells possessed numerous microvilli, which were rather long and sometimes arranged in tufts (Fig. 2). Small apical protrusions were a common finding.

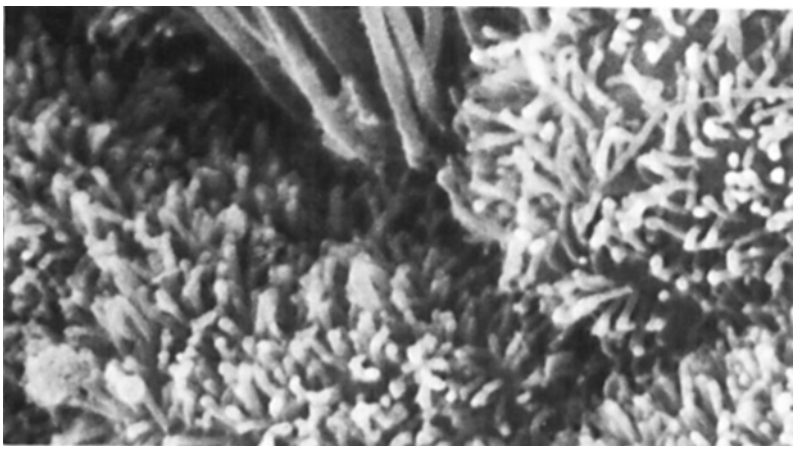

Fig. 2. Endometrial surface after treatment with estriol (Case 10). The cell surfaces possesses many long microvilli. X 11,000.

Estriol-progesterone treated group

Ciliated cells were frequent. The non-ciliated cells possessed fewer microvilli than those in the estriol group. Further, the apical protrusions were larger and more numerous (Fig. 3).

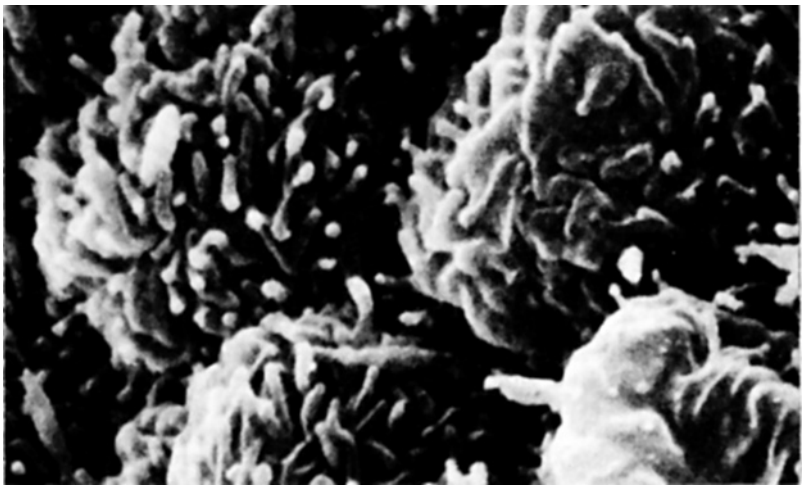

Fig. 3. Endometrial surface after sequential treatment with estriol-progesterone (Case 12). The cell surfaces are irregularly outlined. They are more or less bulging forming small apical protrusions. The microvilli are short and occur in a moderate number. X 11,000.

DISCUSSION

Using the uterine surface ultrastructure as an indicator, it is demonstrated that a response of the target uterine epithelium to estriol is induced both at a lower dose and after a shorter time than has been found earlier (4,6). This apparently occurs in spite of the few hours of elevation of the plasma estriol level after oral administration (3), and might be explained by binding of estriol to the target cell nuclei (2,11). However, since the general knowledge on the relations between plasma levels of various sex hormones and their target organ ultrastructure is meager, it is not possible to relate the proporties of estriol in this respect to those of other hormones.

The schedule of administration used in the present study also seems sufficient to prime the uterine epithelium for a gestagen-induced transformation to a secretory state. Whether vaginal bleedings also can occur in some patients even on short-term and low-dose treatment remains to be ascertained. It is not unreasonable, however, to postulate that the various responses produced by a hormone may have different plasma threshold levels. For instance, a response may occur in the uterine epithelium even if no bleedings are produced. Considering the possibility of a relationship between endometrial

cancer and estrogen replacement therapy in the menopause (13), an action of a hormone on the uterine epithelium has to be evaluated by analysing the responses of this epithelium by as sensitive an indicator as possible.

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