3) Resta P., Nardelli G. B., Ambrosini A., Becagli L., De Salvia D.: "Limits of echography in the evaluation of ovarian tumors ». *Clin. Exp. Obst. Gyn.*, *9*, 165, 1982.
4) Resta P., Nardelli G. B., Ambrosini A., D'Antona N.: "The role of echography in the evaluation of gynecological neoplasia". *Eur. J. Gynaec. Oncol.*, *1*, 1, 1979.
5) Maggino T., Tredese F., Valente S., Marchesoni D., Brandes A., Menighetti M., Onnis G. L.: "Role of second look laparotomy in multidisciplinary treatment and in the follow-up of advanced ovarian cancer". *Eur. J. Gynaec. Oncol.*, *4*, 26, 1983.
6) Maggino T., Ronsisvalle O., Tredese F., Valente S., Brandes A., Onnis G. L., Marchesoni D.: "Role of computed abdominal tomography (C.A.T. scan) in the follow-up of ovarian tumors". *Eur. J. Gynaec. Oncol.*, *4*, 47, 1983

EFFECTS OF ESTRIOL ADMINISTRATION ON HUMAN POSTMENOPAUSAL ENDOMETRIUM

C. MONTONERI - G. ZARBO - A. GAROFALO - S. GIARDINELLA
First Clinic of Obstetrics and Gynecology - University of Catania, Catania (Italy)

Summary: Forty eight women with atrophic endometrium were treated with estriol, 1 mg twice daily, by mouth for a minimum of 10 days and a maximum of 25 days. Vaginal hysterectomy was then performed and specimens were examined histologically. Results showed that estriol produces endometrial hyperplasia in 70.8% of the examined women; only 29.2% of the patients retained atrophic endometrium after treatment.

Key words: estrogen replacement, endometrial hyperplasia, menopause, endometrium.

INTRODUCTION

Estriol has been considered a "weak estrogen" or an "impeded estrogen" for many years ([1, 2]).

Much evidence, concerning the biological effect of estrogens, suggests that uterine responses are correlated to the activity time of the receptor-estrogen complex in the nucleus.

Some experiments support the hypothesis that estriol is unable to promote a sufficient proliferative effect because its intranuclear activity is very short ([3]). Therefore, estriol was classified as "short acting estrogen ([4]).

In many gynecological departments postmenopausal women have been treated with estriol. Dosages varied from 1 mg/day up to 8 mg/day. When estriol was given once a day or in small doses no or minimal effect on the endometrium was found, but trophic activity on the cervix, vagina, urethra, bladder and skin was observed ([4, 5, 6]).

These results were obtained regarding withdrawal bleeding or spotting as the only standard for evaluation of the effect on the endometrial proliferation.

When dilatation and curettage were performed, histological examination showed an atrophic endometrium in most cases. Therefore, withdrawal bleeding or spotting can not be regarded as reliable indices for endometrial proliferation because every kind of endometrium is liable to bleed ([5, 7, 8, 9, 10]).

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XIV, n. 3, 1987

Table 1. — *Data (mean ± S.D.) and endometrial aspects (No., %) regarding patients treated with estriol.*

Endometrial aspects	Patients		Age of patients	Duration of menopause (years)	Period of treatment (days)
Atrophic endometrium	6	23.08	67.33±7.02	17.33±7.02	16.66±3.51
Simple hyperplasia	14	53.85	64.00±5.51	15.00±6.27	16.00±3.51
Cystic hyperplasia	4	15.38	64.00±5.66	15.00±7.07	18.50±9.19
Atypical hyperplasia	2	7.69	74.00±2.83	26.00±4.24	25.00±1.41

On the contrary, several clinical studies and epidemiological investigations confirmed an increased risk of endometrial cancer in postmenopausal women treated with estrogens ([11, 12, 13, 14]).

The aim of the present paper is to study the effects of estriol administration on the human postmenopausal endometrium by histological examination.

MATERIAL AND METHODS

Fifty postmenopausal women scheduled for surgical treatment of uterine prolapse were enrolled for this study. The patients were aged from 55 to 81 years; menopause had occured from 4 to 33 years ago.

Histological examination of the endometrium was performed in all cases before estriol administration.

Two women with endometrial hyperplasia were excluded from the study.

The other 48 women showed atrophic endometrium and received estriol 1 mg twice daily, by mouth, for a minimum of 10 days and a maximum of 25 days; 22 women also received conjugated estrogen locally for vaginal atrophia.

Thereafter, vaginal hysterectomy was performed and specimens were examined histologically.

Statistical analysis was done using chi-square test to study whether the rate of women who developed endometrial hyperplasia was significantly higher in patients associating local conjugated estrogens therapy and oral estriol therapy. Analysis of the results was completed using Student's t test to verify if the endometrial hyperplasia growth had got any relation to the age of patients, to the number of years in menopause and to the treatment days.

RESULTS

Age of patients, duration of menopause, period of treatment, and endometrial aspects after estriol therapy alone or associated with conjugated estrogens therapy are listed in table 1 and in table 2, respectively. After estriol treatment only 6 women (23.08%) out of 26 patients retained an atrophic endometrium, the other 20 patients (76.92%) developed more or less marked endometrial hyperplasia. In particular, 14 women (53.85%) developed simple endometrial hyperplasia, 4 women (15.38%) cystic endometrial hyperplasia and 2 women (7.69%) atypical endometrial hyperplasia (table 1). After estriol therapy associated with local conjugated

Table 2. — *Data (mean ± S.D.) and endometrial aspects (No., %) regarding patients treated with estriol and conjugated estrogens.*

Endometrial aspects	Patients		Age of patients	Duration of menopause (years)	Period of treatment (days)
Atrophic endometrium	8	36.36	71.00±6.78	22.25±6.13	13.25±4.57
Simple hyperplasia	4	18.19	68.00±2.83	19.50±3.53	17.50±3.53
Cystic hyperplasia	8	36.36	67.75±6.13	19.75±6.29	17.75±5.62
Atypical hyperplasia	2	9.09	81.00±1.41	33.00±2.83	20.00±4.24

Table 3. — *Percentage (No., %) of women who retained atrophic endometrium and developed endometrial hyperplasia in two trial groups.*

	Atrophic endometrium		Endometrial hyperplasia	
Estriol therapy	6	23.08	20	76.92
		NS		NS
Conjugated estrogen + estriol therapy	8	36.36	14	63.64

NS, not significant ($p > 0.10$).

estrogens therapy only 8 women (36.36%) out of 22 subjects retained an atrophic endometrium while 14 women (63.64%) developed endometrial hyperplasia: exactly 4 women (18.19%) simple hyperplasia, 8 women (36.36%) cystic hyperplasia, and 2 women (9.09%) atypical hyperplasia (table 2).

Statistical analysis of results carried out by chi-square test did not demonstrate a significant difference between percentages of women who developed endometrial hyperplasia in two trial groups ($p > 0.10$) and that percentage was higher in patients treated with estriol alone (table 3).

Student's t test pointed out endometrial hyperplasia is significantly correlated to the lower mean age ($p < 0.001$) and to the younger mean duration of menopause ($p < 0.001$) of the patients treated with only estriol compared to the subjects treated with conjugated estrogens as well, but is not correlated to the duration of treatment with estriol ($p > 0.10$). In fact, it was slightly longer in the first group of women compared with the second group (table 4).

DISCUSSION

In the present series of patients the estrogenic effect of estriol on the endometrium was clear. Contrary to some other Authors ([15, 16]), our data show that local therapy with conjugated estrogens did not influence the development of endometrial hyperplasia and that estriol promoted endometrial proliferation in postmenopausal women. Infact, more or less marked endometrial hyperplasia appeared in 34 (70.8%) out of 48 patients of the trial according to Heuser *et al.* ([17]) who found an estrogenic effect on the endometrium in 39 out of 40 postmenopausal women when estriol was administered orally. In our study the endometrial proliferation may be due to the fact that estriol was administered twice daily.

The mode of estrial administration may play an important role in the effect of that hormone on the target organs. Repetitive estriol administration during the day results in prolonged elevation of the blood levels of the hormone and in continuous stimulation of estrogen receptors ([4, 8]).

Table 4. — *Correlation between endometrial hyperplasia in two trial groups and age (mean ± S.D.), duration of menopause (mean ± S.D.) and periods of treatment (mean ± S.D.).*

	Age of patients	Duration of menopause (years)	Period of treatment (days)
Estriol therapy	65.54±5.88	16.38±6.44	17.23±4.55
	S	S	NS
Conjugated estrogen + estriol therapy	70.18±6.41	21.82±6.31	16.27±4.82

S, significant ($p < 0.001$); NS, not significant ($p > 0.10$).

Endomertial hyperplasia is considered a potentially premalignant condition, since 1.57% to 25% of cases may progress to endometrial adenocarcinoma [18]. Data available to us indicate that estriol, like other estrogens, can be given without medical indication during the menopausal period. However, estriol is known to behave like a "short acting estrogen" [4], to have a trophic activity on the target organs, to operate on climacteric disturbances [5] and to induce, very rarely, withdrawal bleeding even with endometrial hyperplasia [16]. For those biologic and clinical characteristics estriol can be regarded as one of the less "dangerous" in estrogen replacement therapy in climacteric syndrome and in menopausal disturbances.

A retrospective case-controlled review by Hammond *et al.* [14] demonstrated that cyclic use of estrogen (25 days per month) did not protect patients from development of endometrial adenocarcinoma after 5 years of therapy. When progestin agent was added for 7 to 10 days of each cycle none of the patients thus treated developed endometrial cancer [14, 19]. In fact, progestational agents antagonize the proliferative effects of estrogens by inhibition of the replenishment of the estrogen receptors [20] and induce the enzyme estradiol dehydrogenase, which converts estradiol to estrone [21]. Thus administration of estrogen is elected, some Authors [13, 14, 22] who give them cyclically and combined with a progestagen in the last 7-13 days of the cycle. We are not in agreement since this method of estrogen therapy produces periodical bleeding and that event is not desired in postmenopausal patients.

The indication for administration estrogen to postmenopausal women must be well defined and must be balanced with the potential risks of such therapy.

If estrogen replacement treatment is required, we believe estriol therapy is suitable. The hormone should administered once daily, for a short period and after careful medical examination.

BIBLIOGRAPHY

1) Hisaw F. L., Velardo J. T., Goolsby C. M.: *J. Clin. Endocrinol. Metab., 14*, 1134, 1954.
2) Huggins C., Jensen E. V.: *J. Exp. Med., 102*, 335, 1955.
3) Clark J. H., Peck E. J. jr., Anderson J. N.: *J. Toxicol. Environ. Health., 1*, 561, 1976.
4) Clark J. H., Paszko Z., Peck E. J. jr.: *Endocrinology, 100*, 91, 1977.
5) Kopera H.: «Azione ed efficacia dell'estriolo nella specie umana», Therimas editor: Tavola rotonda sull'estriolo. Roma, p. 35, 1980.
6) Haskins A. L., Moszkowski E. F., Whitelock V. P.: *Am. J. Obst. Gyn., 102*, 665, 1968.
7) Demol R.: «Estriolo: alcuni aspetti clinici», Therimas editor: Tavola rotonda sull'estriolo. Roma, p. 47, 1980.
8) Englund D. E., Johansson E. D. B.: *Acta Obst. Gyn. Scand., 59*, 449, 1980.
9) Myhre E.: *Front. Horm. Res., 5*, 126, 1978.
10) Novak E. R.: "Gynecological and Obstetrical Pathology". Saunders W. B. editor, 2nd ed., 1947.
11) Gray L. A., Christopherson W. M., Hoover R. N.: *Obst. Gyn., 49*, 385, 1977.
12) Weiss N. S., Szekely D. R., Austin D. F.: *N. Engl. J. Med., 294*, 1259, 1976.
13) Brithish Gynaecological Cancer Group: *Lancet, 1*, 1359, 1981.
14) Hammond C. B., Jelovsek F. R., Lee K. L., Creasman W. T., Parker R. T.: *Am. J. Obst. Gyn., 133*, 537, 1979.
15) Campagnoli C., Prelato L., Dolfin A. M.: «Azione a livello endometriale dell'estriolo e, per confronto, degli estrogeni coniugati equini». Therimas editor: Tavola rotonda sull'estriolo. Roma, p. 103, 1980.
16) Englund D. E., Johansson E. D. B.: *Br. J. Obst. Gyn., 85*, 957, 1978.
17) Heuser H. P., Staemmler H. J.: *Arzneim. Forsch. Drug Res., 23*, 558, 1973.
18) Gole H.: "Hyperplasia of the endometrium". In: "The uterus", Herting A. T. and Abel M. R. (eds.), Baltimore, Williams and Wilkins Co., p. 260, 1973.
19) Gambrell R. D. jr., Massey F. M., Castenda T. A., Ugenes A., Ricci L., Wright J.: *Obst. Gyn., 55*, 732, 1980.
20) Hshueh A. J. W., Peck E. J. jr., Clark J. H.: *Endocrinology, 98*, 438, 1976.
21) Tseng G. L., Gurpide E.: *Endocrinology, 97*, 825, 1975.
22) Hammond C. B., Maxson W. S.: *Fertil. Steril., 37*, 5, 1982.