EFFECT OF OESTROGEN AND PROGESTERONE THERAPY ON THE ENDOMETRIUM OF POST-MENOPAUSAL WOMEN

by

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SUMMARY

We studied a group of 398 patients who had been receiving oestrogen replacement therapy since 1976. Group I consisted of 138 patients who received Premarin (Conjugated equine oestrogen, Ayerst) in two different dosages (0.625; 1.25 mg) and progestational agents such as Neogest (Norgestrel, Schering), Duphaston (Dydrogesterone, Duphar) 5 mg and Primolut N (Norethisterone, Schering) 5 mg, for a period ranging from 7 and 21 days. Group II consisted of 106 patients who received Harmogen (Piperazine Oestrone Sulphate, Abbott) in two different dosages (1.5 mg; 2.25 mg) with the above-mentioned progestational agents for a period ranging from 7 and 21 days. Group III consisted of 154 patients who received Progynova (Oestradiol Valerate, Schering) in two different dosage (1 mg; 2 mg) with the above-mentioned progestational agents were added for 7 days. This produced cystic hyperplasia of endometrium. When the duration of progestational agents was increased to 10 days or more, more atrophic and secretory endometrium was produced and there was no incidence of cystic hyperplasia.

Introduction

Approximately 25 per cent of women are sufficiently distressed by climacteric symptoms to warrant oestrogen replacement therapy which has proven to be of benefit in many trials (Campbell and Whitehead, 1977; Studd *et al*, 1977). Nordin *et al* (1975) showed its value in preventing postmenopausal osteoporotic changes and Hammond *et al* (1979a) demonstrated in a randomised controlled study that it has long-term metabolic benefits in significantly reducing the rates of strokes, heart attacks, hypertension, osteoporosis and fractures.

Oestrogens for clinical use have been available for 45 years and have become increasingly popular. The major controversy currently surrounding oestrogen therapy is whether it is safe and in particular whether there is an associated increased incidence of endometrial carcinoma. Many reports from the U.S.A. (Smith *et al*, 1975; Antunes *et al*, 1979 and Hammond *et al*, 1976b) support the view that there is an associa-

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tion of increased incidence of endometrial carcinoma and oestrogen therapy. None includes a group of patients large enough for comment taking progesterone. The study by Antunes *et al* (1979) is particularly important because, for the first time, details of hormone therapy are given. Nonc of his 65 patients with carcinoma of the endometrium received any progestogens, 29 had continuous oestrogen therapy, and 9 were given Stilboestrol. Hammond *et al* (1979b) confirmed an increased incidence of carcinoma of the endometrium with a risk factor of 9.3, but only I of the 11 oestrogen-taking patients with cancer was receiving progestogen rarely during her 24 years of high dose cyclical therapy with Premarin 2.5 mg for gonadal dysgenesis.

Wilson *et al* (1963) and Nachtigall *et al* (1976) did not find any association between oestrogen therapy and endometrial carcinoma.

Studd (1976) argued, such an increase should have led to a rise in deaths from endometrial carcinoma since there has been no radical improvement in the results of treatment of the disease. In fact the apparent doubling of the incidence of endometrial carcinoma has been followed by a halving of the mortality rate perhaps because of misdiagnosis of hyperplasia and over-diagnosis of carcinoma. There remains little agreement about the definition of endometrial pathology and still less about the malignant potential of different types of hyperplasia. Greenblatt (1976) reported that there was no evidence to suggest that oestrogen treatment increased the incidence of endometrial carcinoma. Thom *et al* (1979) reported that there was no case of carcinoma among the 1000 patients who received replacement therapy under their care. During the same period they had 4 cases of endometrial carcinoma referred from outside, 3 had unopposed continuous oestrogen therapy for more than 12 years.

Since there is still controversy about the effect of long-term hormone replacement therapy using oestrogen in the postmenopausal women we studies a group of patients who attended our special menopause clinic since 1976.

Material and Methods

Since 1976 we studied a group of 398 patients who had spontaneous menopause and were receiving hormone replacement therapy for severe climacteric symptoms. The mean age of the patients was 52.8 years (range 45-65) and the mean duration of time that had elapsed following cessation of menstrual cycle was 4.8 years (range 1-12). Serum levels of pituitary gonadotrophins and oestradiol were measured to confirm the climacteric state. All patients had a pretreatment curettage to exclude endometrial pathology such as hyperplasia and adenocarcinoma and only those 398 patients who had no endometrial pathology were given cyclical oestrogen replacement therapy.

Of the 398 patients, 128 patients (32.16%) had no curetting, 110 patients (27.64%) had atrophic endometrium and 160 patients (40.20%) had proliferative endometrium.

Group I — consisted of 138 patients who received Premarin (Ayerst, conjugated equine oestrogen) in two different dosages (0.625 mg; 1.25 mg) with progestational agents such as Neogest (Norgestrel, Schering) 0.5 mg for 7 days (Prempak, Ayerst); Duphaston (Dydrogesterone, Duphar) 5 mg for a period ranging from 7 and 21 days and Primolut N (Norethisterone, Schering) 5 mg for a period ranging from 7 and 21 days. Each regimen of treatment was given for 12 months.

Group II — consisted of 106 patients who received Harmogen (Piperazine oestrone sulphate, Abbott) in two different dosages (1.5 mg; 2.25 mg) with progestational agents such as Duphaston (Dydrogesterone, Duphar) 5 mg for a period ranging from 7 and 21 days and Primolut N (Norethisterone, Schering) 5 mg for a period ranging from 7 and 21 days.

Group III — consisted of 154 patients who received Progynova (Oestradiol Valerate, Schering) in two different dosages (1 mg; 2 mg) with progestational agents such as Norgeston (Levonorgestrel) 0.25 mg for 10 days (Cycloprogynova 1 mg, Schering) and Neogest (Norgestrel) 0.5 mg for 10 days (Cycloprogynova, 2 mg. Schering), Duphaston (Dydrogesterone, Duphar) 5 mg for a period ranging from 7 and 21 days and Primolut N (Norethisterone, Schering) for a period ranging from 7 and 21 days.

Oestrogen replacement therapy was given on a cyclical regimen lasting for 21 out of 28 days and progestational agents were given for a period ranging from 7 to 21 days during the 21 days of oestrogen treatment.

Endometrial curettage was performed under general anaesthetic once a year during the last four days of the 21 days regimen. Initially patients were admitted to the gynaecological ward overnight; since 1980 patients were admitted as day patients. The endometrial curettage was repeated every year if the patients were receiving treatment.

Results

Table I shows the outcome of endometrial curettage from patients who received Premarin and different progestational agents for different periods (Group I).

Two out of 138 (1.45%) patients receiving 0.625 mg of Premarin developed cystic hyperplasia. Of the 138 patients, 116 patients received 1.25 mg of Premarin for a further period of 3 years. Only 2 patients (1.72%) developed cystic hyperplasia of endometrium and all the patients received progestational agents for 7 days ($P < 0.01$). None developed cystic hyperplasia when progestational agents were given for 10 days or more.

Table II shows the outcome of endometrial curetting from 106 patients who received Harmogen and different progestational agents for different periods (Group II).

Of the 106 patients who received 1.5 mg of Harmogen, 2 (1.9%) developed cystic hyperplasia. As the progestational agents were given for a longer period a significant number of patients had no curetting or had atrophic endometrium. The same pattern was noted when the dosage of Harmogen was increased to 2.25 mg. Three out of 81 patients (3.7%) developed cystic hyperplasia ($P < 0.01$).

Table III shows the results on the endometrial curetting from patients who received Progynova and different progestational agents.

Of the 154 patients who received 1 mg of Progynova, 2 developed cystic hyperplasia (1.3%) and both patients received progestational agents only for 7 days.

Of the 154 patients 114 received 2 mg Progynova for a further period of 3 years. Three developed cystic hyperplasia (2.6%) ($P < 0.01$).

TABLE I

The Pattern of Endometrial Curetting from 138 Patients in Group I Receiving Premarin (Conjugated Equine Oestrogen)

Premarin 0.625	No.	Progestational agents		Total duration of treatment (months)	Endometrial curetting				
		Dosage (mg)	Days		N.C. (%)	A (%)	S (%)	P (%)	C.H. (%)
Neogest	42	0.5	7	48	23.8	28.6	19.0	26.2	2.4
Duphaston	48	5.0	7	24	22.9	33.3	18.8	25.0	—
		5.0	10	12	29.2	33.3	16.7	20.8	—
		5.0	21	12	33.3	31.3	16.7	18.8	—
Primolut N	48	5.0	7	24	20.8	25.0	20.8	31.3	2.1
		5.0	10	12	33.3	25.0	20.8	20.8	—
		2.5	21	12	37.5	22.9	20.8	18.8	—
Premarin 1.25 mg									
Neogest	36	5.0	7	36	22.2	27.8	19.4	27.8	2.8
Duphaston	42	0.5	7	12	23.8	28.6	28.6	19.0	—
		5.0	10	12	28.6	30.9	19.0	21.4	—
		5.0	21	12	38.1	19.4	19.0	26.2	—
Primolut	38	5.0	7	12	21.1	28.9	21.1	26.3	2.6
		5.0	10	12	31.6	31.6	21.1	15.8	—
		2.5	21	12	36.8	26.3	15.8	21.1	—

N.C. — No curetting
A — Atrophic endometrium
S — Secretory endometrium
P — Proliferative endometrium
CH — Cystic hyperplasia

TABLE II

The Pattern on Endometrial Curetting from 106 Patients in Group **II** *Receiving Harmogen (Oestradiol Valerate)*

Harmogen 1.5 mg	No.	Progestational agents		Total duration of treatment (months)	Endometrial curetting				
		Dosage (mg)	Days		N.C. (%)	A (%)	S (%)	P (%)	C.H. (%)
Duphaston	58	5.0	7	24	31.0	27.6	17.2	20.7	3.4
		5.0	10	12	34.5	22.4	22.4	20.7	—
		5.0	21	12	41.4	25.9	25.9	15.5	—
Primolut N	48	5.0	7	24	41.7	22.9	18.8	16.7	—
		5.0	10	12	45.8	20.8	20.8	12.5	—
		2.5	21	12	50.0	20.8	14.6	14.6	—
Harmogen 2.25 mg Duphaston	39	5.0	7	12	30.8	25.6	17.9	20.5	5.1
		5.0	10	12	35.9	25.6	20.5	17.9	—
		5.0	21	12	41.0	23.1	23.1	10.3	—
Primolut N	42	5.0	7	12	28.6	33.3	19.0	16.7	2.4
		5.0	10	12	33.3	23.8	21.4	21.4	—
		2.5	21	12	42.9	19.0	21.4	16.7	—

N.C. — No curetting
A — Atrophic endometrium
S — Secretory endometrium
P — Proliferative endometrium
CH — Cystic hyperplasia

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The Pattern of Endometrial Curetting from 154 Patients in Group III Receiving Progynova (oestradiol valerate)

Progynova 1 mg	No.	Progestational agents		Total duration of treatment (months)	Endometrial curetting				
		Dosage (mg)	Days		N.C. (%)	A (%)	S (%)	P (%)	CH (%)
Norgeston	52	0.25	10	36	32.7	28.8	15.4	19.2	3.8
Duphaston	48	5.0	7	24	33.3	25.0	20.8	20.8	—
		5.0	10	12	33.3	29.2	18.8	18.8	—
		5.0	21	12	37.5	29.2	18.8	14.6	—
Primolut N	54	5.0	7	24	22.2	29.6	25.9	22.2	—
		5.0	10	12	29.6	29.6	22.2	18.5	—
		2.5	21	12	37.0	29.6	14.8	18.5	—
Progynova 2 mg									
Neogest	38	5.0	10	36	31.6	26.3	26.3	10.5	5.3
Duphaston	36	5.0	7	12	38.9	22.2	22.2	16.7	—
		5.0	10	12	38.9	25.0	19.4	16.7	—
		5.0	21	12	41.7	27.8	16.7	13.9	—
Primolut N	40	5.0	7	12	30.0	30.0	22.5	15.0	2.5
		25.0	10	12	35.0	27.5	20.0	17.5	—
		2.5	21	12	40.0	25.0	20.0	15.0	—

N.C. — No curetting
A — Atrophic endometrium
S — Secretory endometrium
P — Proliferative endometrium
CH — Cystic hyperplasia

Discussion

Addition of progestogen to oestrogen treatment to prevent endometrial hyperplasia and carcinoma has long been advocated by Greenblatt (1976). Whitehead *et al* (1977) reported that unopposed cyclical oestrogen therapy was associated with endometrial hyperplasia, whereas oestrogen and progestogen combination did not prodce the hyperplastic changes. Gambrell (1978) stated there were 3 endometrial cancer among 1028 patients who received only oestrogen (2.9:1000) as compared with no endometrial cancer among 2552 patients when oestrogen and progestogen were given. Incidence of cancer and endometrial hyperplasia were slightly higher when cyclical oestrogen alone was given and it was very low when oestrogen and progesterone were given to postmenopausal women. Also the endometrial hyperplasia was reversed to normal endometrium in the majority of patients when progestogens were given for 2 or more months (Campbell *et al,* 1978; Whitehead *et al,* 1977 and Paterson *et al,* 1980).

Unopposed oestrogen treatment produces only focal shedding of the endometrium and most of the stimulated endometriun remains for further continued oestrogen stimulation, whereas addition of progesterone produces complete shedding of endometrium. Protective effect of progestogens is also questioned in the recent paper by Jick *et al* (1979). He stated that 7 out of 42 cases of endometrial cancer were in women who had a combined oestrogen and progestogen preparation.

Atypical endometrial change co-existing with adenocarcinoma was thought to be the precursor of malignancy. The adenomatous hyperplasis was believed to be associated with excess oestrogen stimulation in both benign and malignant tissues. There was also an association between prolonged oestrogen stimulation and cystic hyperplasia. There was a possible causative link between some types of endometrial hyperplasia and cancer in susceptible individuals such as those who had abnormal internal secretion of oestrogen, those with infertility, those who had heavy peri-menopausal bleeding and late menopause. The role of ovarian hormones in endometrial carcinoma was first suspected on the basis of observations of certain endocrine disorders such as polycystic ovarian syndrone (Somers *et al,* 1949) and hormone secreting ovarian tumours (Larson, 1954).

We studied a group of 398 patients who received Premarin (Conjugated equine oestrogen), Harmogen (Piperazine oestrone sulphate) and Progynova (Oestradiol valerate) in two different dosages, each for a period of 3 years. The duration of progestational agents varied between 7, 10 and 21 days. Each regimen was given for 12 months and endometrial curettage was done following each regimen to assess the response. When progestational agent was given for 7 days few developed cystic hyperplasia. When it was given for longer periods 30 to 40 per cent of patients had no curetting and an eqal number had atrophic endometrium. None of the 398 patients developed adenomatous hyperplasia or adenocarcinoma. We now routinely add progestational agents for a period of 10 days or more. Patients who developed cystic hyperplasia were given progestational agents for 21 days and the repeat endometrial curettage showed either atrophic or secretory changes.

Continuous oestrogen therapy, particularly in high doses, may produce cancer of the uterine body in women who are susceptible. Well supervised combined hormone therapy for the climacteric syndrome should not produce an increased risk of endometrial pathology. Longer term the-

rapy must have added progestogen and endometrial sampling in the form of vabra curettage or conventional diagnostic curettage should be performed every year or whenever there is irregular bleeding in patients taking unopposed oestrogen.

Since there is much controversy about the effect of oestrogen on endometrium in the postmenopausal women, it is important to evaluate the use of oestrogen and use a small dosage regimen combined with progestational agents for 10 days or more to relieve climacteric symptoms.

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