Effect of Natural Oestrogens on Blood Pressure and Weight in Postmenopausal Women

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SUMMARY

An investigation of the effect of conjugated oestrogens (USP) on the blood pressure and weight gain of postmenopausal women was undertaken. Fifty-one unselected women were treated for one year with cyclically administered conjugated oestrogen. Both the mean systolic and diastolic blood pressures of those in the group increased, but only the diastolic was significantly elevated. Individual evaluation revealed that this was largely owing to an idiosyncrasy among certain women. Age is probably a predisposing factor, for hypertension occurred more frequently among the older women. The significance of the change in blood pressure is commented upon, and the recommendation that postmenopausal women on oestrogen replacement therapy should have their blood pressure measured every 6 months is made.

Weight gain is not affected by long-term treatment with conjugated oestrogens.

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Of the various undesirable clinical effects attributed to oral contraceptives, blood pressure response and weight gain are two which can be measured. It has been confirmed that in certain women, there is a definite relationship between the development of hypertension and the use of oral contraceptives.[1] The incidence of hypertension (blood pressure greater than 140/90 mmHg) in women who were previously normotensive, and who are taking oral contraceptives, is about 5%[1], but it varies in some series from less than 2%[2] to as much as 18%[3]. More recently, Spellacy and Birk[4] found that only oral contraceptives which contained synthetic oestrogens induced elevations of blood pressure above 140/90 mmHg, and that the natural oestrogens were free from this effect. All their patients had intact functioning ovaries. Since some authors[6] have reported a significant correlation between systolic blood pressure and the age of women on the pill, it was decided to study the effect of the long-term use of natural oestrogens on the blood pressure of a group of unselected postmenopausal women.

A less clear relationship exists between weight gain and the use of the oral steroid contraceptives.[6] Most women care about their weight and since weight gain is also an age-related problem, it was thought desirable to determine whether there is a relationship between oestrogen replacement therapy in menopausal women, and a gain in weight.

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PATIENTS AND METHODS

The group studied comprised 51 White women who were attending a Climacteric Clinic, and who were selected at random without prior measurement of their blood pressure or weight. All appeared to be in good health. Their mean age was 51 years (range 31 - 68 years) and their mean weight was 64,86 kg (range 42,64 to 111,13 kg). The duration of the postmenopausal period varied from 6 months (surgical menopause) to 24 years, with a median of 7,3 years. Each woman served as her own control; the statistics were, however, based on the response of the group. The blood pressure was recorded after a period of rest, while the patient was sedentary. The recordings were based on the first and the last sounds. To compensate for the group's mean age and the effect of nervousness, blood pressures in excess of 150 mmHg systolic and 90 mmHg diastolic were regarded as abnormal. If both systolic and diastolic values were abnormal, the patients were classified as hypertensive. There were 10 patients with hypertension, 6 of whom were being treated with hypotensive drugs. At each examination, the patients were weighed at about the same time of day and in the same clothes. No specific instructions were given regarding the daily diet. After the initial evaluation of the patients, conjugated oestrogen, usually 1,25 mg/d of Premarin, was prescribed for 3 weeks on a cyclic basis, and the measurements were repeated at 3 and 9 months (Table I). After a year's therapy, medication was omitted for a month and the blood pressure and weight were measured as before.

TABLE I. MEAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE (mmHg) IN A GROUP OF POSTMENOPAUSAL WOMEN BEFORE, DURING, AND AFTER TREATMENT WITH NATURAL OESTROGEN

	Baseline	3 months' treatment	9 months' treatment	No treatment
Systolic				
Mean	134,09	136,12	138,82	141,38
Variance	591,01	405,25	459,19	264,90
SEM	3,58	2,58	3,00	2,37
Diastolic				
Mean	79,04	82,96	83,20	88,30
Variance	235,00	148,29	146,76	122,04
SEM	2,24	1,72	1,70	1,60

The matched pairs *t* test determined whether there were any statistically significant changes in blood pressure and weight, by calculation of (*a*) baseline observations to the 3-month treatment value; (*b*) baseline to the 9-month treatment interval; (*c*) baseline values to the post-treatment level; and (*d*) the 9-month assessment to the post-treatment test time (Tables II, III and IV). In all cases, the earlier reading was subtracted from the later so that a positive mean change implied an increase of the characteristic. The *t* values were interpreted using Bonferroni's inequality procedure.

TABLE II. STATISTICAL SIGNIFICANCE OF THE ALTERATION IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE (mmHg) IN A GROUP OF POSTMENOPAUSAL WOMEN BEFORE, DURING, AND AFTER TREATMENT WITH NATURAL OESTROGEN

	3 months' baseline	9 months' baseline	Post-treatment baseline	Post-treatment 9 months
Systolic				
Mean	2,63	4,09	5,30	2,19
Variance	506,33	863,64	658,40	646,85
SEM	3,32	4,29	3,91	3,71
t	0,79	0,95	1,36	0,59
P	NS	NS	NS	NS
Diastolic				
Mean	4,35	3,62	7,44	4,94
Variance	249,30	274,20	277,78	215,19
SEM	2,33	2,42	2,54	2,14
t	1,87	1,50	2,93	2,31
P	NS	NS	$<0,05$	NS

TABLE III. MEAN WEIGHT (kg) IN A GROUP OF POSTMENOPAUSAL WOMEN BEFORE, DURING AND AFTER TREATMENT WITH NATURAL OESTROGEN

	Baseline	3 months' treatment	9 months' treatment	No treatment
Mean	65,20	65,39	65,25	65,07
Variance	407,8	371,31	386,04	374,50
SEM	1,90	1,81	1,85	1,84

TABLE IV. STATISTICAL SIGNIFICANCE OF WEIGHT CHANGE

	3 months' baseline	9 months' baseline	Post-treatment baseline	Post-treatment 9 months
Mean	0,18	0,04	−0,38	−0,37
Variance	11,33	29,40	30,50	10,60
SEM	0,31	0,51	0,52	0,30
t	0,59	0,09	−0,72	−1,20
P	NS	NS	NS	NS

RESULTS

After 3 months of treatment with conjugated oestrogens, the mean systolic blood pressure of the group increased slightly from the baseline value of 134,09 ± 3,58 to 136,1 ± 2,58 mmHg. The mean values continued to increase thereafter and reached 138,82 ± 3,00 mmHg at the 9-month treatment interval, and 141,38 ± 2,37 mmHg a month after treatment had been suspended (Table I). The difference in the systolic blood pressure at these time intervals was not statistically significant (Table II).

The mean diastolic pressures also increased — the respective baseline, 3-month, 9-month, and 'no-treatment' values were 79,04 ± 2,24, 82,96 ± 1,72, 83,20 ± 1,70 and 88,30 ± 1,60 mmHg. The *t* value for the change in the diastolic blood pressure from the baseline observation to the no-treatment measurement was significant at the 5% level. Much of this increase probably occurred between the 9-month and the post-treatment observation: the *t* value on the latter difference would, on its own, be significant ($P<0,01$), but if it is regarded as one of a set of 12 *t* values (according to Bonferroni's inequality procedure), it falls just short of statistical significance.

Therefore although both the mean systolic and diastolic blood pressures for the group increased during the 13-month test period, only the change in diastolic pressure was significant after a year's (and a possible 9 months') treatment. The mean diastolic value was still within normal limits.

In the above statistical evaluation there was a distinct variation in the individual blood pressure responses to the conjugated oestrogens. Thus, 8 of the normal subjects (who had initial blood pressures below 150/90 mmHg) had systolic blood pressures in excess of 150 mmHg in the 'no-treatment' period and 7 patients experienced this at the 9-month test interval. The systolic pressures in these women ranged from 155 to 180 mmHg. The same was true for alteration in the diastolic pressure, as 7 women had values above 90 mmHg at 3 months; 4 after 9 months, and 7 after completion of the study. The diastolic pressures varied between 95 and 110 mmHg. One patient, aged 54, reacted remarkably to treatment: from an initial value of 130/70 mmHg, her blood pressure rose to a 190/102 mmHg at 3 months and remained elevated (180/90 mmHg at 9 months). Her blood pressure settled to 130/90 mmHg one month after treatment was stopped.

By contrast, there were 10 women who were hypertensive at the onset of the trial. Six were being treated with antihypertensives. Without adjusting this treatment, no fewer than 8 were unaffected by the added oestrogen therapy. The remaining 2 increased either their systolic or their diastolic pressures or both, by about 20 and 10 mmHg, respectively.

Although the total number of patients studied is small, it appears that age may influence the blood pressure response. For example, 60% (3 out of 5) of the women over the age of 60 had an increase in blood pressure; the same was true for 46,6% and 37,5% of those between the ages of 50 and 60 years, and 40 and 50 years, respectively. The blood pressure in women under the age of 40 years was unaffected, and this applied also to 2 women with baseline essential hypertension.

There was no consistent relationship between the initial weight and the blood pressure response to treatment with oestrogen.

Weight

Despite the 13-month duration of the study, the mean body weight of the group remained surprisingly constant, and varied by less than 0,45 kg (Table III). Approximately 20% were obese patients and weighed more than 72,5 kg. Their reaction to oestrogen was no different from that of the women in the study who were not obese. The same was true for individual weight gain.

DISCUSSION

The steroid contraceptives are associated with an increased incidence of hypertension.[1,7] Although many of the earlier reports were based on retrospective analyses[8,9] there have since been a number of planned prospective studies that have shown a significant rise in the systolic, but not the diastolic pressure, in women to whom these agents have been given.[2,4,5,11] This increase in blood pressure is not related to the progestogen component of the pill, since no increase in blood pressure has been found in women taking progesterone alone,[4,10] while a more recent study has shown that the change in blood pressure when combined preparations are used, is not related to their progestogenic potency.[11]

Oestrogen, given singly or as one constituent of a contraceptive, is associated with an increase in blood pressure. Thus, in a recent controlled study, Spellacy and Birk[4] showed that hypertension (blood pressure >140/90 mmHg) occurred in previously normotensive women who were using combined oral contraceptives (5%), mestranol (6%), and ethinyl oestradiol (7%), but not in controls who were using the intra-uterine device (IUD) or progestogens, or in women who were taking conjugated oestrogens. Other authors[12,13] have also reported a rise in blood pressure during oestrogen administration, but the cause of this pressure increase is not known. Walters and Lim[14] postulated that the increase in blood volume and cardiac output in women on oral contraceptives may be the factor. Crane *et al.*[13] and Saruta *et al.*[3] noted an increase in blood renin substrate and renin activity in women who were taking oral contraceptives, and they suggested that this change might be induced by oestrogens alone, but not by progestogens.[13] Recently, Catt *et al.*[15] reported that oral contraceptives elevate radio-immunoassayable blood angiotensin-II levels, and Tapia *et al.*[16] have suggested that the development of hypertension during oral contraceptive therapy may arise from abnormal inactivation of the angiotensin. Whatever the mechanism involved, the same effect has not been reported in women who are taking conjugated oestrogen.[4]

The incidence of benign essential hypertension is greater in middle-aged women than in men, and it also increases with age. This is especially pertinent in view of the widespread prophylactic and long-term use of oestrogen in the treatment of certain conditions, such as osteoporosis, which are related to the menopause. Despite the fairly extensive literature which relates oestrogen therapy to hypertension in women of reproductive age, there is relatively little available information about postmenopausal women. Lauritzen[17] noted that natural oestrogens did not induce hypertension when given to climacteric women, and Spellacy and Birk[4] concluded that women treated with conjugated oestrogen did not develop hypertension. Closer scrutiny of their results, however, revealed that approximately 20% of their subjects did develop diastolic pressure in excess of 90 mmHg after 6 months' treatment with conjugated oestrogen.

The mean diastolic blood pressure for the group in this study was significantly raised ($P<0,05$) after therapy had been suspended after a year's treatment with conjugated oestrogens. Their absolute values were, however, not markedly elevated — a maximal diastolic pressure of 110 mmHg was recorded on occasion in only 4 women. The group's mean systolic blood pressure was not significantly altered. A number of isolated instances of malignant hypertension associated with oral contraceptives have been noted. In one report,[18] the blood pressure rose to 230/140 mmHg in a previously normotensive woman and returned to normal when the oral contraceptive was discontinued; 9 months later the oral contraceptive was resumed and hypertension returned. Conversely, small groups of women with severe hypertension or hypertension associated with chronic nephritis, experienced no evident deterioration of the condition while taking oral contraceptives. It would therefore appear that certain women have an idiosyncratic response to oestrogen with an elevation of blood pressure, whereas others are unaffected.

Assessment of each patient in this investigation showed that some responded to conjugated oestrogen by isolated elevations of either the systolic or the diastolic pressure or of both pressures and that this effect frequently persisted for a month after treatment had been suspended. However, 8 of the 10 women who were hypertensive at the beginning of the study, maintained their blood pressure while on therapy.

Age may be a related factor, since abnormal elevations of blood pressure occurred more frequently in older women. Clezy *et al.*[5] noted the same factor in their prospective study of the use of oral contraceptives and concluded that the older the patient, the more likely a rise in blood pressure. A history of hypertension in pregnancy or a familial history of the disease, may indicate the women who are more likely to develop hypertension when they take oral contraceptives.[7] Obesity has often been associated with the degree of blood pressure response to oral contraceptives;[19] in the present series, weight *per se* was not found to be a related factor.

Abnormal blood pressure response to oral contraceptives usually returns to normal once the treatment is discontinued. In this study there were 8 normotensive women who were left with blood pressures in excess of 150/90 mmHg after oestrogen therapy. All, however, were measured within a month of suspension of treatment. Further follow-up is necessary to evaluate the permanence of the vascular response in these women, since the time taken for the pressure to fall after stopping oral contraceptives is often as long as 3 months.[11] The significance of hypertension associated with oral contraceptives (oestrogen) must be viewed objectively. With few exceptions, the risk of severe hypertension appears to be low. Nevertheless statistics of mortality and morbidity suggest

that even relatively small increases of blood pressure carry a distinct risk.[20] Therefore, although the increase in blood pressure reported in most prospective surveys has not been accompanied by clinical complications, it would be prudent to measure the blood pressure at 6-monthly intervals, if not more frequently, when the patient is already hypertensive.

Weight gain is an effect of ageing and it is, therefore, more difficult to evaluate. Spellacy *et al.*[21] reported a significant increase in weight during 6 months' treatment with mestranol, ethinyl oestradiol, and conjugated oestrogen. This increase was unrelated to age and was as great in premenopausal as in postmenopausal women. However, in another report by the same investigators, women using the IUD were also found to have a progressive increase in weight when observed for 12 months. Similarly, Goldzieher *et al.*[6] reported that 30% of their patients on placebos gained 2,5 kg or more compared with 19% to 31% of patients who took (combined and sequential) oral contraceptives. It is alleged that some 50% of menopausal women gain weight and that this exceeds 2,5 kg in 20% of women, and 5 kg in 29%.[17] Conjugated oestrogens did not affect the weight of patients in the present study, in spite of their mean age of 51 years and weight of 64,86 kg. Utian[22] examined 50 patients before and after oöphorectomy, and also found no increase in weight after one year of oestrogen substitution therapy.

CONCLUSION

This study has shown that some postmenopausal women have an idiosyncratic response to oestrogen replacement therapy in that they react with elevations of blood pressure that may frequently affect either the systolic or the diastolic component. The permanence of this effect could not be determined, because the patients were not followed up for a sufficiently long time after suspension of therapy. Age may be an important associated factor, as the hypertensive reaction occurred more frequently among the older women in the group. Although the increase in blood pressure in most instances was not great, even when small, it may increase the morbidity. It is, therefore, recommended that the blood pressure of postmenopausal women on oestrogen replacement therapy should be measured at 6-monthly intervals. Essential hypertension does not appear to be an absolute contra-indication to prophylactic oestrogen replacement therapy, since the majority of women in the present series who had 'baseline' hypertension were not adversely affected.

Weight is unaffected by the long-term use of conjugated oestrogens.

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