PAPERS AND ORIGINALS

Blood Pressure in Women Taking Oral Contraceptives

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Summary

A controlled prospective survey of women taking oestrogen-progestogen oral contraceptives showed increases in mean systolic and diastolic blood pressure of 14.2 mm Hg and 8.5 mm Hg respectively after four years. The largest increases in individual cases were 36 mm Hg systolic and 20 mm Hg diastolic. Blood pressure returned to pre-treatment levels within three months after oral contraceptives had been stopped. These changes in blood pressure were unrelated to the progestogenic potencies of the preparations being taken.

Introduction

In 1969 a prospective controlled study of the effect of oral contraceptives on blood pressure was set up jointly by the Glasgow clinic of the Family Planning Association and the M.R.C. Blood Pressure Unit. The blood pressures of women taking combined oestrogen-progestogen contraceptives were compared with those of a control group using cervical diaphragms or intrauterine contraceptive devices. The results after one year (Weir *et al.*, 1971 a) showed a mean increase of 6.6 mm Hg in systolic pressure in the group taking oral contraceptives with no significant change in diastolic pressure. This paper presents the results after three and four years.

Patients and Methods

Details of these have been given previously (Weir *et al.*, 1971 a). Since the earlier report two other brands of oral contraceptives

had been included and the following drugs had been studied: (a) ethynodiol diacetate 1 mg, mestranol 0.1 mg (Ovulen) (from 1969 to 1970 only); (b) norethisterone 1 mg, mestranol 0.05 mg (Norinyl-1); (c) megestrol acetate 4 mg, ethinyloestradiol 0.05 mg (Volidan); (d) lynestrenol 2.5 mg, ethinyloestradiol 0.05 mg (Minilyn); (e) norethisterone acetate 3 mg, ethinyloestradiol 0.05 mg (Gynovlar 21).

Eighty-three women had taken oral contraceptives and 48 had used mechanical methods of contraception for three years. Ten in the oral contraceptive group and seven in the control group had been followed up to four years. Defaulting from follow-up was unlikely to be an important source of bias (Weir *et al.*, 1971 a). The difference in age on admission to the survey between the oral contraceptive group (mean 23.1, S.D. $\pm$ 3.4 years) and the control group (mean 28.1, S.D. $\pm$ 7.5 years) was also unlikely to have influenced the results (Weir *et al.*, 1971 a). Previous pregnancies had occurred in 13 women taking oral contraceptives and in 25 women using mechanical methods of contraception—this difference in parity was also unlikely to be a source of bias (Weir *et al.*, 1971 a).

Results

After four years systolic blood pressure had increased in every woman who had taken oral contraceptives, the largest individual rise being 36 mm Hg. The mean systolic pressure showed a significant increase of 14.2 mm Hg (table 1, fig. 1). Diastolic blood pressure rose in seven and fell in three of these women, the largest increase being 20 mm Hg and the mean rise 8.5 mm Hg (table I, fig. 2). In the control group no significant change occurred in either systolic or diastolic blood pressure (table I, figs. 1 and 2).

Analysis of the 83 women who were followed up for three years showed a similar general increase in blood pressure—mean systolic pressure (fig. 3) had risen by 9.2 mm Hg (S.E. $\pm$ 0.81) and diastolic pressure by 5.0 mm Hg (S.E. $\pm$ 0.79). The highest systolic pressure reached in these women was 155 mm Hg, representing an increase of 28 mm Hg. Diastolic pressure did not exceed 90 mm Hg in any subject. The blood pressure changes after three years have not been related to changes in weight ($r=0.18$; $P>0.1$) nor to a past history of renal disease ($\chi^2=1.14$; $P>0.1$), a family history of hypertension ($\chi^2=2.36$; $P>0.1$), parity ($\chi^2=3.3$; $P>0.05$), social class ($\chi^2=7.58$; $P>0.1$), or cigarette smoking ($\chi^2=1.03$; $P>0.1$). Only two of

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TABLE 1—Changes in Mean Blood Pressure and Weight ($\pm$ S.E.) after Four Years in Women taking Oral Contraceptives or using Mechanical Methods of Contraception

	Oral Contraceptives			I.U.C.D. or Diaphragm		
	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Weight (Kg)	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Weight (Kg)
Before using contraceptive	107.3 $\pm$ 1.9	63.9 $\pm$ 1.8	57.9 $\pm$ 1.1	108.7 $\pm$ 2.5	67.1 $\pm$ 4.2	54.9 $\pm$ 3.0
After 4 years of using contraceptive	121.5 $\pm$ 2.2	72.4 $\pm$ 2.7	60.3 $\pm$ 1.3	106.7 $\pm$ 2.4	65.4 $\pm$ 2.7	54.7 $\pm$ 3.2
Statistical significance						
Paired <i>t</i> test	5.16	3.02	2.71	0.70	0.92	0.09
P	<0.001	<0.02	<0.05	>0.1	>0.1	>0.1

FIG. 1—Mean systolic blood pressure ($\pm$ S.E.M.) after four years in a group of women taking oral contraceptives and in control group using mechanical methods of contraception. FIG. 2—Mean diastolic blood pressure ($\pm$ S.E.M.) after four years in group of women taking oral contraceptives and in control group using mechanical methods of contraception.

FIG. 3—Changes in systolic blood pressure after three years in women taking oral contraceptives and in control group using mechanical methods of contraception.

FIG. 4—Mean changes in blood pressure ($\pm$ S.E.M.) after stopping oral contraceptives.

our cases had had pregnancy hypertension of whom one showed an increase and one a decrease in blood pressure after taking oral contraceptives for three years.

In 32 women who had taken oral contraceptives for between one and three years and then stopped treatment blood pressure had returned to pretreatment levels within three months, the mean systolic pressure falling by 9.7 mm Hg ($P < 0.001$) and the diastolic pressure by 2.9 mm Hg ($P < 0.05$) compared with the measurements made one month before stopping (fig. 4).

The effect on blood pressure of oral contraceptives with different progestogenic concentrations is shown in table II. A comparison of women taking norethisterone 1.0 mg with women taking norethisterone 3.0 mg showed no statistical difference in the changes in systolic ($t=0.92$; $P > 0.1$) or diastolic ($t=0.77$;

TABLE II—Changes in Blood Pressure after Two Years in Women taking Oral Contraceptives Containing Different proportions of progestogen

Oral Contraceptive	No. of Women Using Contraceptives	Change in Systolic B.P. (mm Hg)		Change in Diastolic B.P. (mm Hg)	
		Mean	$\pm$ S.E.	Mean	$\pm$ S.E.
Mestranol (0.05 mg) and norethisterone (1 mg)	44	8.1	1.3	4.0	1.0
Ethinylloestradiol (0.05 mg) and lynestrenol (2.5 mg)	38	8.1	1.0	1.7	0.9
Ethinylloestradiol (0.05 mg) and norethisterone (3 mg)	32	9.7	1.1	5.0	1.4
Ethinylloestradiol (0.05 mg) and megestrol (4 mg)	19	4.2	2.1	1.8	1.6
Controls (I.U.C.D. or Diaphragm)	48	-1.4	1.2	-0.8	0.8

$P > 0.1$) pressure though both of these preparations were associated with greater rises of diastolic pressure than the other two combinations. From these results there is no evidence to suggest that an increase in progestogenic potency is associated with a larger change in blood pressure.

Discussion

The results of this further analysis have confirmed our previous report (Weir *et al.*, 1971 a) of a rise in systolic blood pressure in women taking oestrogen-progestogen oral contraceptives. Rises in diastolic pressure became statistically significant two years after starting treatment. Both rises of pressure are generally readily reversible (fig. 4). These findings are in accord with other series (Carmichael *et al.*, 1970; Spellacy and Birk, 1972; Clezy *et al.*, 1972) but the rises in blood pressure are not as great as those reported under less standardized conditions (Saruta *et al.*, 1970; Crane *et al.*, 1971).

Two studies have suggested that oral contraceptives are more likely to induce changes in blood pressure in women with a history of pre-eclampsia (Spellacy and Birk, 1972; Clezy *et al.*, 1972), though Smith (1972) did not confirm these findings. The data in the present prospective survey are still insufficient for us to comment about this, but elsewhere we have reported on 23 isolated cases of marked rises in blood pressure associated with taking oral contraceptives where there was no evidence that previous pre-eclampsia was a contributing factor (Weir *et al.*, 1974). Though a role for sodium and water retention in producing the initial rise in blood pressure has not so far been excluded, we have found no relation between the changes in blood pressure and changes in weight ($r = 0.18$; $P > 0.1$) or in sodium, potassium, or water balance (Weir *et al.*, 1971 b).

No increase in blood pressure has been found in women taking progestogen only (MacKay *et al.*, 1971; Spellacy and Birk, 1972), and the present study has shown that the changes in blood pressure are not related to the progestogenic potency of the combined preparations used. A rise in blood pressure during oestrogen administration, however, has been reported (Lim *et al.*, 1970; Crane *et al.*, 1971; Spellacy and Birk, 1972), and possibly the increase in blood volume, cardiac output, and blood pressure in women taking combined oral contraceptives

(Walters and Lim, 1970) may be induced by the oestrogen component. To date, the effect of preparations with different oestrogenic potencies has not been adequately studied.

The increases in blood pressure in this prospective survey have not so far been accompanied by clinical complications and would not generally be regarded as clinically important. Nevertheless, mortality and morbidity statistics, mostly obtained for men (Pickering, 1968; Kannel *et al.*, 1971), suggest that a relatively small increase of blood pressure within the range found in this study carries a distinct risk. Possibly, therefore, prolonged administration of oestrogen-progestogen oral contraceptives may lead to levels of blood pressure which may increase morbidity and affect life expectancy.

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Interaction between Doxycycline and Barbiturates

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Summary

In a cross-over study of five hospitalized patients the half life of doxycycline was significantly shortened after 10 days' treatment with phenobarbitone. In five patients on continuous barbiturate therapy the half life of doxycycline was even shorter. Barbiturates or other agents inducing drug metabolism should be used cautiously in combination with doxycycline, since this might result in therapeutically inadequate serum concentrations of the antibiotic.

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Introduction

For treatment with bacteriostatic agents to be successful the serum antibiotic level must not fall below the minimum inhibitory concentration. Certain drugs interfere with the gastrointestinal absorption of tetracyclines (Waisbren and Hueckel, 1950; Neuvonen *et al.*, 1970). Hepatic metabolism seems to be important in the elimination of doxycycline and the drug does not accumulate significantly in renal insufficiency (Klinger *et al.*, 1970). Barbiturates and many other commonly used preparations stimulate metabolism of drugs through inducing hepatic microsomal enzyme activity (Breckenridge and Orme, 1971; Remmer, 1972; Prescott, 1973). The present study aimed to discover whether barbiturates modify the half life of doxycycline in man.

Patients and Methods

Ten chronically ill patients volunteered as subjects for the study. Their usual daily medication of digitalis and diuretics and, in