

Oral contraceptives and hypertension

*An epidemiological survey*¹

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The effect of oral contraceptive medication on blood pressure was studied in 74 young married women over a period ranging from 3 months to 2 years.

A rise in mean systolic pressure of 7 mmHg and in mean diastolic pressure of 1.81 mmHg was observed. The increase in systolic pressure was significant. Furthermore, the relation between systolic pressure and age became significant during oral contraceptive therapy.

Three out of 74 women developed sustained systolic and diastolic hypertension during oral contraceptive therapy.

Women with a history of hypertension in pregnancy or with a history of parental hypertension showed a greater incidence of hypertensive visits during oral contraception.

Earlier reports on an apparent association between oral contraceptive therapy and the aggravation or onset of hypertension (Woods, 1967; Laragh *et al.*, 1967) have led to studies to investigate the incidence of hypertension in women taking oral contraceptives. Goodlin and Waechter (1969), in a retrospective survey, found no hypertension in women taking oral contraceptives. Wallace (1971) found that the incidence of oral contraceptive use in women attending a hypertensive clinic was twice that expected among the population at large, and Clezy (1970) reported that, in 8 patients, resistance to conventional antihypertensive therapy occurred during administration of oral contraceptives. However, these surveys were not definitive studies to determine the true incidence of hypertension in women taking oral contraceptives.

In a controlled study, Tyson (1968) reported an incidence of onset of hypertension of 15.5 per cent in 51 subjects studied for periods up to 8 months, while Saruta, Saade, and Kaplan (1970) studied 62 women (6 of whom were already hypertensive) before and after oral contraception. Of the 56 normotensive women in this latter study, 10 developed hypertension. Both of these surveys

show a high incidence in the onset of hypertension during oral contraceptive medication. However, Weir, Tree, and Fraser (1969) studied 69 women for 2 months and 31 women for 4 months and observed no sustained hypertension.

This paper reports the results of a prospective study which was undertaken to determine the incidence of onset of hypertension in women taking oral contraceptives, and to examine more closely the association between oral contraceptive therapy and changes in blood pressure. An attempt was also made to correlate the changes in blood pressure during therapy with the age and weights of the subjects and the length of time over which the contraceptive was administered.

Methods

Selection of subjects Seventy-seven women were studied in this survey, 74 of whom began oral contraceptive therapy. None had received oral contraceptive therapy for at least 10 months before the onset of this investigation. All were married and were aged between 17 and 40 years. At an initial interview with patients the following clinical data were obtained: age, number of pregnancies, number of live children. Information was also obtained in a number of the women of a past history of hypertension, renal disease, hypertension in pregnancy, and a family history of hypertension.

Oral contraceptive therapy was begun in 74 subjects and consisted of Eugynon (62 subjects),

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norethisterone (2 subjects), ethynodiol (3 subjects), Serial C (3 subjects), lynoestrenol 2.5 (1 subject), and not recorded (3 subjects).

Procedure for clinical examination The patients were examined throughout by their own physician. Each had at least one examination before beginning oral contraceptive therapy. After beginning therapy visits were at approximately 3-monthly intervals. The period of observation ranged from 3 months to 2 years. During clinical examination the patients were weighed, their urine tested for the presence of protein and glucose, and arterial pressure measured.

Patients were rested for 30 minutes before determining arterial pressure using an epidemiological sphygmomanometer which avoids observer bias in the determination of systolic and diastolic pressure. Three measurements were made over a period of 5 minutes.

Treatment of individual data Systolic hypertension was defined arbitrarily as a systolic pressure of greater than 150 mm and diastolic hypertension as a diastolic pressure of greater than 90 mmHg. These definitions are referred to as clinical systolic or diastolic hypertension, respectively. In order to relate this arbitrary definition of hypertension to the population studied, hypertension was also defined statistically and the two compared. A systolic or diastolic pressure of greater than 2 standard deviations about the respective means was defined as statistical systolic or diastolic hypertension. The range of 2 standard deviations about the mean incorporates 95 per cent of the population if the distribution of this population is normal. The mean of the three arterial pressure recordings obtained at each visit was used in calculating the results.

The mean systolic pressure and mean diastolic pressure were determined from the data in 77 women before the onset of oral contraceptive therapy and used as control data.

FIG. 1 Distribution of patients according to number of visits during oral contraceptive therapy.

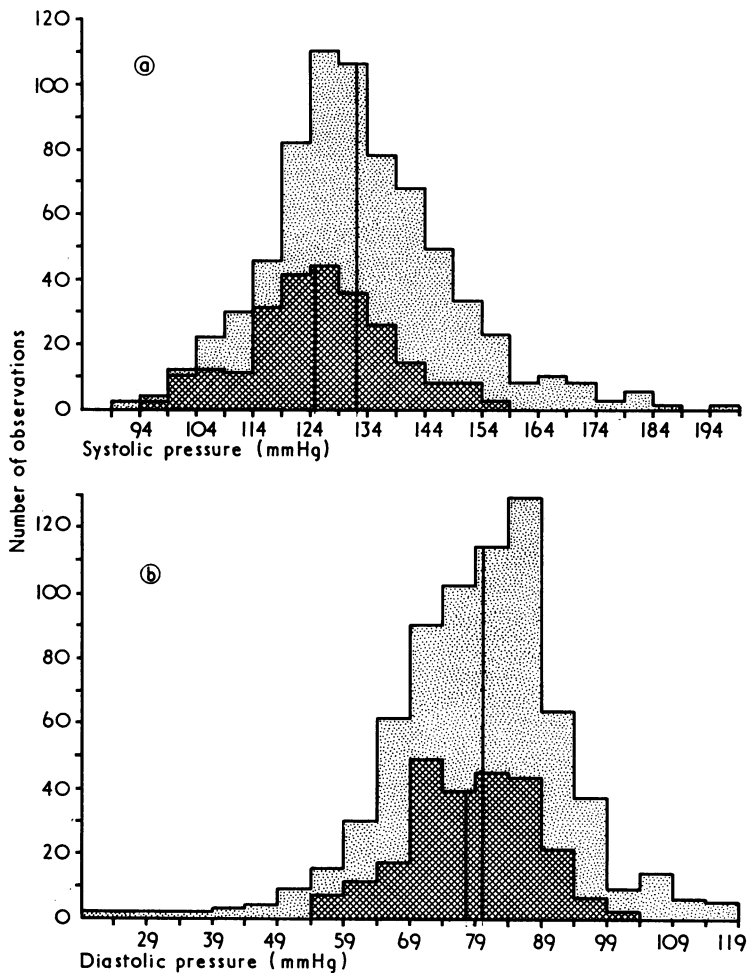
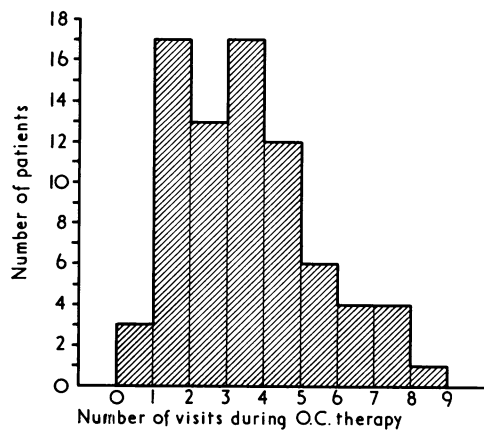


FIG. 2a Histograms and means of systolic blood pressures in subjects before (oblique hatching) and during (stippling) oral contraceptive therapy.

FIG. 2b Histograms and means of diastolic blood pressures in subjects before (oblique hatching) and during (stippling) oral contraceptive therapy.

An excessive increase in systolic pressure was defined as a pressure increase greater than 25 mmHg above that recorded at the first visit and in diastolic pressure as an increase of more than 15 mmHg.

The number of visits during oral contraception at which clinical systolic or diastolic hypertension alone, and both systolic and diastolic hypertension occurred was determined. The relation between past history (if known) and the presence or absence of hypertension during contraceptive therapy was also determined. Hypertension in pregnancy was diagnosed if the arterial pressure was greater than 150/90 mmHg or the diastolic

pressure was greater than 95 mmHg during pregnancy.

Treatment of massed data Histograms for systolic pressure and diastolic pressure, with class intervals of 5 mmHg, were calculated from the data of all the control (before oral contraception) visits and from that for all visits during oral contraceptive therapy. The means and standard deviations were determined. Tests for normality, for skewness, and for kurtosis were performed using first and second cumulants. Simple linear regressions were calculated between the following variables.

a) *Control data:*

Systolic pressure: age.
Diastolic pressure: age.
Systolic pressure: weight.
Diastolic pressure: weight.

b) *Data obtained after beginning oral contraceptive (OC) therapy:*

Systolic pressure: age.
Diastolic pressure: age.

Relative weight increase was determined by the following formula:

$$\frac{\text{Mean weight on OC} - \text{before OC weight}}{\text{OC weight}} \times 100.$$

Mean increase in systolic pressure during contraceptive therapy was determined in each subject by the following formula:

$$\frac{\text{Mean systolic pressure on OC} - \text{before OC systolic pressure.}}{\text{before OC systolic pressure.}}$$

Mean increase in diastolic pressure during oral contraceptive therapy was determined for each individual using a similar formula.

Student's t-test was used to determine whether the increase in systolic pressure and diastolic pressure was significantly different from 0.

Linear regression analyses were calculated between the following variables.

Mean systolic pressure increase: relative weight increase.
Mean diastolic pressure increase: relative weight increase.
Mean systolic pressure increase: length of time of administration of oral contraceptive.
Mean diastolic pressure increase: length of time of administration of oral contraceptive.
Relative weight increase: length of time of administration of oral contraceptive.
Mean systolic pressure increase: age.
Mean diastolic pressure increase: age.

The criteria which had to be fulfilled before a patient was classified as having hypertension due

to the administration of oral contraceptives were:

- 1) No previously recorded history of hypertension (with the exception of hypertension in pregnancy).
- 2) Non-hypertensive at the control visit. (Systolic and diastolic pressure must be below 150 mmHg and 90 mmHg, respectively.)
- 3) Clinical systolic or diastolic hypertension recorded at more than one visit.
- 4) Clinical hypertension recorded at (n-1) visits, where n = the total number of visits during the administration of oral contraceptives.
- 5) Statistical hypertension at (n-2) visits during the administration of oral contraceptives.

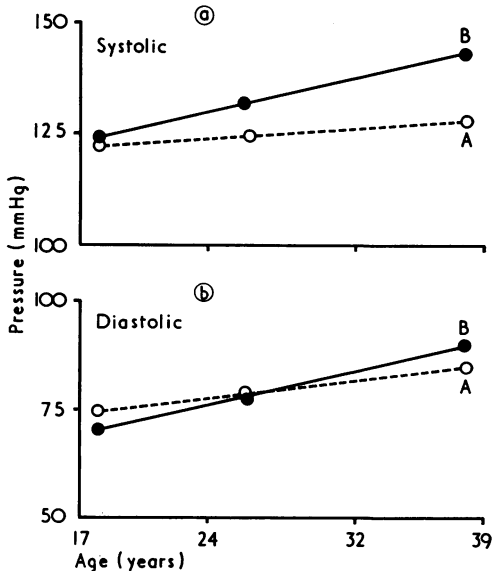
Results

Of the 77 patients who initially attended the clinic, 74 began oral contraceptive therapy. The distribution of the subjects according to the number of visits during oral contraceptive therapy is shown in Fig. 1.

The distributions and means of systolic and diastolic pressure in subjects before and during oral contraceptive therapy are shown in Fig. 2a and 2b, respectively. The mean control systolic pressure of 77 subjects was 125.42 mmHg, with a standard deviation of 12.07 mmHg, and the corresponding figures for the diastolic pressure were 77.45 and 10.08, respectively. These values were calculated from 240 observations. During oral contra-

FIG. 3a Correlation between systolic pressure and age. (A) Control data ($F=1.64$; NS). (B) During oral contraception ($F=6.22$; $r=0.30$; $P<0.05$).

FIG. 3b Correlation between diastolic pressure and age. (A) Control data ($F=7.28$; $r=0.32$; $P<0.01$). (B) During oral contraception ($F=11.02$; $P<0.01$).



ceptive therapy 686 observations were obtained. The means and standard deviations were as follows: systolic pressure, 132.37 and 15.12; diastolic pressure, 80.26 and 12.16.

The increase in systolic pressure during oral contraceptive therapy was significant when tested by Student's paired t-test ($P < 0.001$). There was no significant increase in diastolic pressure.

Linear regression analysis of control data revealed a positive correlation between weight and systolic pressure ($F = 17.15$, $r = 0.44$, $P < 0.001$) (74 subjects), but not between age and systolic pressure ($F = 1.64$) (68 subjects; Fig. 3a). There was also a positive correlation between weight and diastolic pressure ($F = 8.28$, $r = 0.32$, $P < 0.01$), and there was a significant correlation between age and diastolic pressure ($F = 7.28$, $r = 0.32$, $P < 0.01$) (Fig. 3b).

During the administration of oral contraceptives, systolic pressure now became significantly correlated with age ($F = 6.22$, $r = 0.30$, $P < 0.05$) (Fig. 3a), while the correlation between age and diastolic pressure persisted ($F = 11.02$, $P < 0.01$) (Fig. 3b).

Though both systolic pressure and diastolic pressure correlated significantly with age, there was no significant correlation between either mean increase in systolic pressure or mean increase in diastolic pressure with age; nor was there any significant relation between either the mean systolic pressure increase or the mean diastolic pressure increase and the length of time of administration of the oral contraceptive agent.

There was no significant increase in weight during oral contraceptive therapy, tested with Student's paired t-test (70 subjects), nor was there any significant relation between relative weight increase and length of time of administration of oral contraceptives ($F = 3.0877$). No significant correlation existed between relative weight increase and mean increase in systolic pressure ($F = 0.37$), nor between mean increase in diastolic pressure and relative weight increase ($F = 0.0265$).

Individual data The incidence of clinical systolic hypertension (i.e. systolic pressure > 150 mmHg) and of clinical diastolic hypertension (i.e. diastolic pressure > 90 mmHg) in the control period before the administration of oral contraceptive therapy was 1.19 per cent and 6.49 per cent, respectively. No patient had a rise in both systolic and diastolic pressure.

The percentage of individuals with at least one hypertensive visit (systolic, diastolic, or both) during oral contraception, as determined by clinical and statistical definition, is shown in Table 1. This Table also shows the percentage of individuals with an increase in systolic pressure greater than 25 mmHg and in diastolic pressure greater than 15 mmHg recorded during one or more visits during oral contraception. While good agreement is obtained between clinical and statistical criteria of systolic hypertension, this is not so with diastolic hypertension.

Using the criteria described for defining the onset of hypertension in women taking oral contraceptives, 6 women developed sustained systolic hypertension and 3 of these also developed sustained diastolic hypertension. The clinical details and mean systolic and diastolic pressure before and during oral contraception are shown in Table 2. Of the 74 women studied, 8.1 per cent developed sustained systolic hypertension and 4.05 per cent developed sustained systolic and diastolic hypertension.

Table 3 shows the relation between the occurrence of one or more clinical hypertensive visits during oral contraception and the presence or absence, where known, of a history of hypertension in pregnancy, of renal disease, of proteinuria, or of a family history of hypertension. Those with a parental history of hypertension and those with a history of hypertension in pregnancy showed a considerably greater incidence of hypertension than women who were known to have no such history.

TABLE 1 Percentage of population with one or more clinical hypertensive visits and statistical hypertensive visits before and during oral contraception

	Clinical			Statistical			Excess increase		
	Incidence of hypertension								
	Systolic	Diastolic	Systolic and diastolic	Systolic	Diastolic	Systolic and diastolic	Systolic pressure	Diastolic pressure	Systolic and diastolic pressure
Before therapy	1.29	6.49	0	—	—	—	—	—	—
During oral contraception	28.37	22.97	22.97	20.27	13.51	6.75	14.86	9.45	2.7

TABLE 2 Clinical data from 3 women with both systolic and diastolic hypertension and a further 3 women with systolic hypertension

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	28	25	26	29	29	35
Parity	2	2	3	2	3	3
Systolic hypertension	+	+	+	+	+	+
Diastolic hypertension	+	+	+	-	-	-
Mean control systolic pressure	128.6	135.3	139.6	147.6	130.6	136.6
Mean OC systolic pressure	168	183.5	165.8	152.6	150.7	153.6
Increase in systolic pressure	39.4	48.2	26.2	5.0	20.1	17.0
Mean control diastolic pressure	84.3	87.0	89.3	82.6	89.0	85.0
Mean OC diastolic pressure	98.3	113	107	79.8	90.2	88.3
Increase in diastolic pressure	14.0	26.3	17.7	-	-	-
Blood pressure during pregnancy	160/110	150/110	150/110	170/80	-	140/105
Family history	M+F*	M+F*	-	-	M*	-
Albuminuria	+	-	+	-	-	+
Post-pill systolic pressure	133.7	156	161.5	-	-	-
Post-pill diastolic pressure	87	106	109.8	-	-	-
Time after stopping OC of 1st blood pressure record	4/12	12/12	4/12	-	-	-

OC, during oral contraceptive therapy.

* M, maternal history of hypertension; F, paternal history of hypertension.

Discussion

An ideal study would have compared a matched group of women using an equally effective form of contraception other than the pill. Since no equally effective, nonoperative method exists, and since women at the time of the study generally refused other forms of contraception, it was not possible to obtain a matched control group. Therefore, in this study, special care was taken with the control (before OC) measurements, since within-subject comparisons formed the bases of most of the subsequent analyses.

In the control data, a significant correlation emerged between the weight of the subject and both the systolic and diastolic pressure, whereas only diastolic pressure was correlated with age. However, during oral contraceptive administration, a significant rise in mean systolic pressure occurred ($P < 0.001$), and a significant correlation emerged ($F = 6.22$, $r = 0.30$, $P < 0.05$) between the rise in systolic pressure and age (the age of the subject used was that at the first visit). The change in this correlation during oral contraceptive therapy indicates that the older the subject, the more likely is the systolic pressure to rise with this therapy, though the correlation between mean increase in systolic pressure and age within individuals during oral contraceptive therapy did not become significant ($F = 3.6086$). The frequency distribution of the systolic pressure in the control data was normal. However,

after oral contraceptive therapy, the frequency distribution became both skewed to the right and peaked. This may indicate the presence of two populations differing in their response to oral contraceptive therapy.

During oral contraceptive therapy, there was no significant increase in the mean diastolic pressure, nor was there any relation between mean increase in diastolic pressure and either age or relative weight increase. The frequency distributions for diastolic pressures of control and oral contraceptive data were both skewed to the left. In addition, the oral contraceptive frequency distribution was peaked (Fig. 2b). This may be at least partly due to variability of measurement of diastolic pressure through the difficulty in gauging the second sound on auscultation.

TABLE 3 Incidence of hypertensive visits during oral contraceptive therapy in those patients with known positive or negative histories of renal disease, hypertension during pregnancy, proteinuria, or parental hypertension

Condition	Negative history		Positive history	
	No.	% hypertensive	No.	% hypertensive
Renal disease	9	11	10	20
Hypertension during pregnancy	40	23	26	58
Proteinuria	8	25	9	33
Parental hypertension	27	30	19	53

One problem in this study has been the relation between the prevalence of hypertension based on clinical or statistical criteria. Since a systolic pressure of >150 mmHg was the criterion for diagnosis of clinical hypertension and a pressure of >149.56 mmHg was the criterion for statistical hypertension, it is not surprising that good agreement for the prevalence of both types of systolic hypertension was obtained. However, whereas the criterion for clinical diastolic hypertension was >90 mmHg, that for statistical diastolic hypertension was >97.61 mmHg. This accounts for the greater prevalence of clinical as compared to statistical diastolic hypertensive visits. For this reason, in the determination of the onset of sustained hypertension during oral contraceptive therapy, a less rigid criterion was applied to the statistical data as compared to the clinical data.

Of the 74 women studied, 6 developed systolic hypertension and 3 of the 6 had diastolic hypertension as well. In these 3 women, oral contraception was withdrawn after a maximum of 3 visits partly because all experienced physical discomfort and partly because of the raised arterial pressure. Of these women, only one (Case 1, Table 2) has returned to non-hypertensive levels after cessation of oral contraception. Cases 2 and 3 have persistent raised arterial pressure, though in Case 2 this is asymptomatic.

Two points emerge from consideration of the data obtained from these 3 women (Table 2). First, the increase in both systolic and diastolic pressure occurred within 3 to 4 months after oral contraceptive therapy began, and was sustained. Furthermore, since the correlation between the mean increase in systolic and diastolic pressure and the length of time of administration of oral contraceptive therapy was not significant, it is suggested that the hypertension induced by oral contraceptive therapy is of rapid onset. Secondly, all 3 women had a record of hypertension during pregnancy (Table 2). The association between hypertension in pregnancy and hypertension during oral contraception is further strengthened by the finding that 58 per cent of women with a positive history of hypertension in pregnancy had at least one hypertensive visit during oral contraception as compared to a prevalence of 23 per cent in women with a negative history of hypertension in pregnancy. Saruta *et al.* (1970) also noted a conspicuous association between hypertension in pregnancy and the onset of hypertension in women on oral contraceptive medication. There is also a greater incidence of one or more hypertensive visits during oral con-

traceptive therapy in women with a parental history of hypertension (53%) than in those with no such history (30%) (Table 3).

The prevalence of sustained hypertension (4.05%) in this population was much lower than the 15.5 per cent in the study of Tyson (1968) and the 18 per cent in that of Saruta *et al.* (1970). The reason for the disparity is most likely to be due to differences in the diagnostic criteria for hypertension. Another obvious difference is that the women in this study belonged to a semirural community of European extraction.

Our findings indicate that those women who have a parental history of hypertension or a history of hypertension during pregnancy are more likely to become hypertensive during oral contraceptive therapy. Furthermore, the development of hypertension is likely to occur soon after beginning oral contraception. Finally, there is a great need for an internationally accepted definition of hypertension for use in epidemiological surveys so that prevalence can be compared in different populations and surveys.

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References

- Clezy, T. M. (1970). Oral contraceptives and hypertension: the effect of guanethidine. *Medical Journal of Australia*, **1**, 638.
- Goodlin, R. C., and Waechter, V. (1969). Oral contraceptives and blood-pressure. *Lancet*, **1**, 1262.
- Laragh, J. H., Sealey, J. E., Ledingham, J. G. G., and Newton, M. A. (1967). Oral contraceptives. Renin, aldosterone, and high blood pressure. *Journal of the American Medical Association*, **201**, 918.
- Saruta, T., Saade, G. A., and Kaplan, N. M. (1970). A possible mechanism for hypertension induced by oral contraceptives. *Archives of Internal Medicine*, **126**, 621.
- Tyson, J. E. A. (1968). Oral contraception and elevated blood pressure. *American Journal of Obstetrics and Gynecology*, **100**, 875.
- Wallace, M. R. (1971). Oral contraceptives and severe hypertension. *Australian and New Zealand Journal of Medicine*, **1**, 49.
- Weir, R. J., Tree, M., and Fraser, R. (1969). Effect of oral contraceptives on blood pressure, and on plasma renin, renin substrate, and corticosteroids. *Journal of Clinical Pathology*, **23**, Suppl. 3, 49.
- Woods, J. W. (1967). Oral contraceptives and hypertension. *Lancet*, **2**, 653.

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