Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 961–964. Pergamon Press. Printed in Great Britain.

# CONTRACEPTIVE STEROIDS AND HYPERTENSION

R. J. WEIR,* D. L. DAVIES, R. FRASER, J. J. MORTON, M. TREE and A. WILSON

M.R.C. Blood Pressure Unit and Department of Medicine, Western Infirmary, Glasgow G11 6NT, Scotland

## SUMMARY

In a prospective controlled study mean systolic blood pressure had risen by 10·2 mmHg and mean diastolic pressure by 6·0 mmHg after 2 yr in 186 women taking oestrogen-progestogen oral contraceptives. After 5 yr, 15 of these women showed mean increases of 12·3 mmHg systolic and 8·8 mmHg diastolic. The greatest rise in systolic pressure was 41 mmHg and the highest systolic level reached was 168 mmHg. In two cases diastolic pressure increased by 34 and 24 mmHg to 94 and 98 mmHg respectively.

In a second study no significant correlation was found between blood pressure and concurrent plasma concentrations of renin, renin-substrate, angiotensin II, aldosterone, cortisol or DOC in women taking oestrogen-progestogen steroid contraceptives. Total exchangeable sodium and potassium were not affected by oral contraceptive administration and there was no correlation between total exchangeable sodium and blood pressure.

## INTRODUCTION

There now seems no doubt that combined oestrogen-progestogen oral contraceptives induce a rise in blood pressure in most women [1–4]. The time of onset and extent of this increase varies between individuals and only occasionally does the blood pressure rise to levels which may be associated with clinical symptoms and signs [5–7, 25). However, as more women take these steroid preparations for longer periods of time, the possible long-term hazards must be constantly reviewed.

This paper will describe the latest results of two studies, a controlled prospective epidemiological survey of the changes in blood pressure induced by oestrogen-progestogen oral contraceptives which was started in Glasgow in 1969 (Study 1), and an investigation of the possible mechanisms for these changes (Study 2).

Some of these results have been discussed elsewhere [4, 7–10].

## METHODS

*Study 1*

Details of the epidemiological survey have been given elsewhere [4, 8]. The oral contraceptives used in this study have been.

Ethynodiol Diacetate 1·0 mg. Mestranol 0·1 mg (Ovulen 100), Norethisterone 1·0 mg Mestranol 0·05 mg (Norinyl), Lynestrenol 2·5 mg Ethinyl Oestradiol 0·05 mg (Minilyn), Norethisterone 3·0 mg, Ethinyl Oestradiol 0·05 mg (Gynovlar-21), Megestrol 4·0 mg Ethinyl Oestradiol 0·05 mg (Volidan).

The control group of women used mechanical methods of contraception, either a cervical diaphragm or intra-uterine contraceptive device (I.U.C.D.).

Of the women taking oral contraceptives, 15 have now been followed-up for 5 yr, 48 for 4 yr and 186 for 2 yr. In the control group 10 women have been followed up for 5 yr, 41 for 4 yr and 60 for 2 yr.

*Study 2*

In another group of women taking oral contraceptives but not part of the prospective survey, intravenous samples were taken in the morning after the subject had been recumbent for 30 min. Some of these women had been referred with markedly raised blood pressure. Diet was not restricted, and none of these women was receiving a diuretic or hypotensive drug. The following measurements were made: Plasma renin concentration [11], plasma renin-substrate concentration [12], plasma angiotensin II concentration [13], plasma aldosterone and cortisol concentration [14, 15], plasma DOC concentration [16] and total exchangeable sodium [17]. Results were analysed by Student's t-test.

## RESULTS

*Study 1*

As shown in Fig. 1, five yr after starting oestrogen-progestogen oral contraceptives the mean systolic blood pressure in 15 women had risen by 12·3 mmHg, ($P < 0·01$) whereas no significant change had occurred in the control group of 10 women ($P > 0·1$). This change in systolic pressure in the oral contraceptive group became statistically significant ($P < 0·05$) after 1 yr and continued to increase significantly for a further year ($P < 0·01$). The rise thereafter became less pronounced and the level at 5 yr was not significantly different from that at 2 yr ($P > 0·1$).

Mean diastolic pressure in the oral contraceptive group showed a more gradual increase (Fig. 2), reaching statistical significance after 2 yr, ($P < 0·01$) the overall mean increase at 5 yr being 8·8 mmHg. No

* Present address: Gartnavel General Hospital, Glasgow G12 0YN, Scotland.

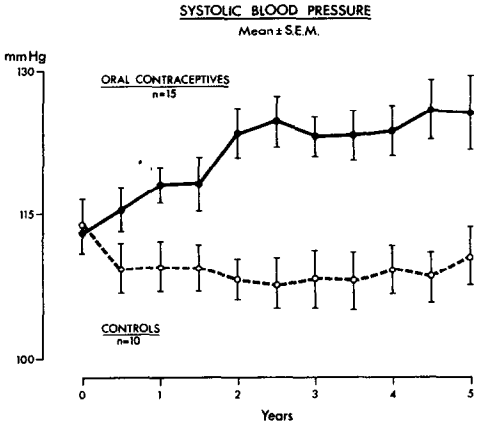


Fig. 1. Changes in systolic blood pressure after 5 yr in women taking oral contraceptives and in a control group of women using intra-uterine contraceptive devices or cervical diaphragms.

significant change occurred in the control group ($P > 0{\cdot}1$) after 5 yr.

Figure 3 illustrates the changes in systolic blood pressure after 2 yr in 186 women taking oral contraceptives, compared to a control group of 60 women. The histogram shows that there was an overall shift in the oral contraceptive group which reflected a general increase in systolic pressure, the difference between the two groups being statistically significant at the 1% level. Diastolic blood pressure showed a similar general increase in the oral contraceptive group, the difference from the control group being statistically significant at the 5% level. Although some women showed increases of up to 41 mmHg systolic and 34 mmHg diastolic while others showed a slight fall in pressure, there was no evidence at this stage to suggest that there was a distinctly separate group of women who were more sensitive to the effects of oral contraceptives than the general female population being studied.

325 women taking oestrogen-progestogen oral contraceptives have been followed-up for between 6

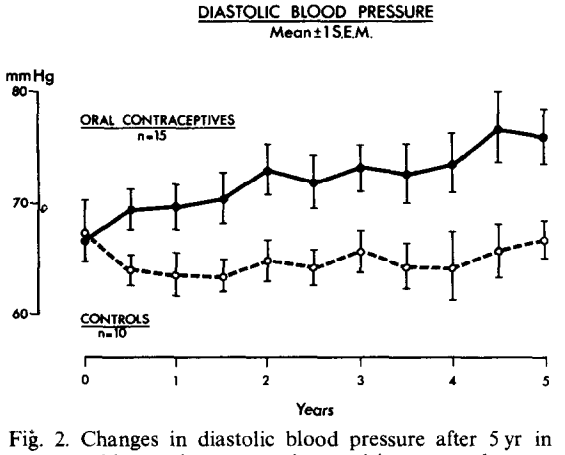


Fig. 2. Changes in diastolic blood pressure after 5 yr in women taking oral contraceptives and in a control group of women using intra-uterine contraceptive devices or cervical diaphragms.

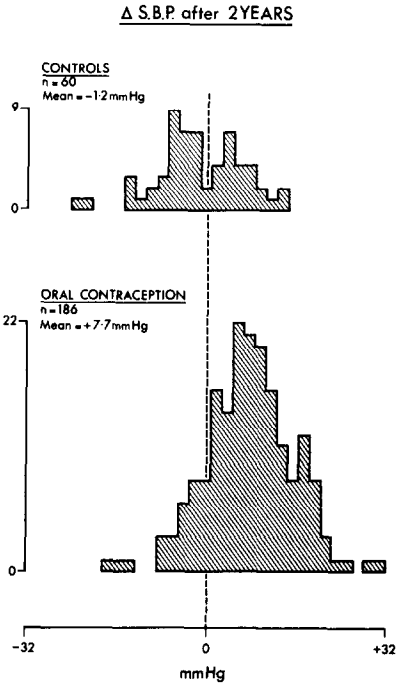


Fig. 3. Changes in systolic blood pressure after 2 yr in women taking oral contraceptives and in a control group of women using intra-uterine contraceptive devices or cervical diaphragms.

months and 5 yr. Of these, 8 have shown increases in systolic pressure to above 140 mmHg (to between 141 and 168 mmHg., representing increases of 5 to 41 mmHg). Diastolic pressure has risen to over 90 mmHg. in 2 cases (94 and 98 mmHg., representing increases of 34 and 24 mmHg respectively). In no case to date has there been any apparent clinical complication associated with the changes in blood pressure.

*Study* 2

No significant correlation was found between systolic or diastolic blood pressure and the concurrent circulating levels of renin, renin-substrate, angiotensin II, aldosterone, cortisol or DOC (Table 1). The plasma concentrations of renin-substrate, cortisol and DOC were elevated in many women taking oral contraceptives irrespective of blood pressure levels, as has been described in previous papers [7, 8, 10].

No significant change occurred in total exchangeable sodium ($P > 0{\cdot}1$) or total exchangeable potassium ($P > 0{\cdot}1$) when measured in 5 women during and three months after stopping oestrogen-progestogen oral contraceptive administration.

Total body water increased in two women and decreased in one after stopping oral contraceptives, the mean showing an insignificant increase of 13 ml/kg. No relationship was demonstrated between total exchangeable sodium and blood pressure (Table 1), and there was no evidence of an abnormal relationship between total exchangeable sodium and plasma angiotensin II concentration in women taking oral contraceptives (Fig. 4).

Table 1. The relationships between blood pressure and plasma concentrations of renin, renin-substrate, angiotensin II, aldosterone, cortisol and DOC and NaE in women taking oestrogen-progestogen oral contraceptives.

| | | RENIN | RENIN SUBSTRATE | ANGIOTENSIN II | ALDOSTERONE | CORTISOL | DOC | NaE |
|---|---|---|---|---|---|---|---|---|
| SYSTOLIC | r | 0.16 | 0.02 | 0.13 | 0.28 | 0.40 | 0.01 | 0.23 |
| | p | >0.1 | >0.1 | >0.1 | >0.1 | >0.1 | >0.1 | >0.1 |
| DIASTOLIC | r | 0.11 | 0.04 | 0.15 | 0.21 | 0.07 | 0.35 | 0.26 |
| | p | >0.1 | >0.1 | >0.1 | >0.1 | >0.1 | >0.1 | >0.1 |
| | n | 39 | 35 | 40 | 17 | 17 | 20 | 11 |

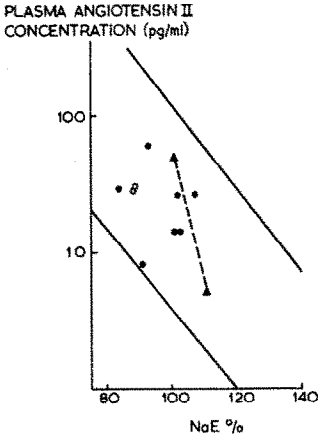


Fig. 4. The relationship between angiotensin II concentration and total exchangeable sodium in women taking oral contraceptives. ● Individual cases. ○——○ ▲----▲ represent values during and after oral contraceptive administration in 2 women. Parallel lines show ± 2 S.D. of values for normotensive subjects not taking oral contraceptives.

## DISCUSSION

There is now good evidence from a number of studies that oestrogen-progestogen oral contraceptives induce statistically significant rises in both systolic and diastolic blood pressure in most women [1–4]. The results of the present prospective controlled survey suggest that this increase in blood pressure generally occurs in the first 2 yr of oral contraceptive administration, although in some women it continues to rise progressively for at least 5 yr (Fig. 5).

It is possible that there is a subgroup of women who are more sensitive than the general female population to the vascular effects of oral contraceptives but the data from this prospective survey to date do not support this. Other studies have suggested that the women who have greater rises of blood pressure while taking oral contraceptives are those who would be more likely to develop hypertension spontaneously—that is those who are older and heavier, those with a history of hypertension in pregnancy and those with a family history of high blood pressure [2, 3]. However, this does not appear to be the case in the Glasgow survey [4].

Although the administration of oestrogen-progestogen oral contraceptives may be associated with malignant phase hypertension (5, 25), the incidence of severe clinical complications so far reported is low [1–4, 7, 18–20]. Most of these studies, however, have been of short duration and it seems possible that prolonged administration of these contraceptive steroids may in some women lead to levels of blood pressure which carry a risk of clinical complications.

No increase in blood pressure has been found in women given oral progestogens alone [3] and changes in blood pressure in our prospective survey were not related to the progestogenic potency of the combined preparations being used [4]. Administration of oral oestrogens, especially ethinyl oestradiol, in doses equivalent to those used in the combined oral contraceptive can cause significant increases in blood pressure [3]. Oral oestrogens also cause haemodynamic changes similar to those induced by combined oestrogen-progestogen steroids, i.e. increased plasma volume, stroke volume and cardiac output [21, 26]. It seems likely, therefore, that

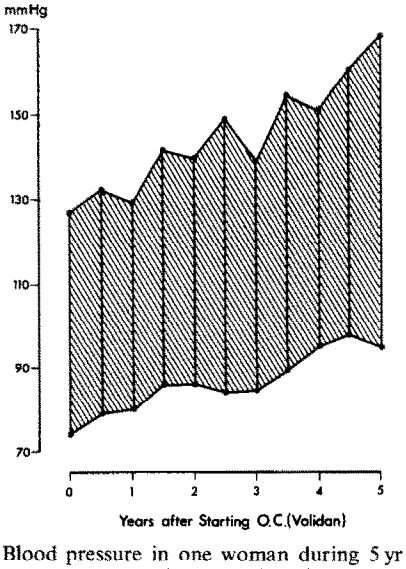


Fig. 5. Blood pressure in one woman during 5 yr of oral contraceptive administration.

the oestrogenic component is responsible for the elevated pressure, by the haemodynamic changes which are produced.

To our knowledge there is no published report relating the severity of the changes in blood pressure to the magnitude of the increases in plasma volume or cardiac output.

Steroid contraceptives may be associated with raised plasma concentrations of the vasopressor agent angiotensin II [22]. We have not confirmed this finding and we have found no evidence to suggest that the rise in blood pressure is related to an increase in circulating levels of angiotensin II, renin or renin-substrate (Table 1).

In general, women taking oestrogen-progestogen oral contraceptives gain weight and occasionally develop mild ankle oedema. These signs, in conjunction with the increased plasma volume, suggest that there may be fluid and sodium retention due to excess mineralocorticoid activity. In contradistinction to another study [23] our results showed no significant change in plasma aldosterone concentration in women taking contraceptive steroids; and no significant relationship existed between the altered blood pressure and the circulating levels of aldosterone, cortisol or DOC.

Previously we have demonstrated no relationship between the changes in blood pressure and changes in weight [4] and the present study has shown no increase in total exchangeable sodium or total body water in the small number studied. Also we have been unable to demonstrate a significant relationship between total exchangeable sodium and blood pressure in these women.

Circulating levels of angiotensin II inappropriately high in relation to concurrent sodium balance may be responsible for hypertension associated with the malignant phase or with chronic renal failure [24]. From our present data there is no evidence to suggest that this is the reason for hypertension induced by oral contraceptives.

According to the present data, the renin-angiotensin system does not appear to be involved in the blood pressure changes associated with oestrogen-progestogen oral contraceptives, nor do the corticosteroids aldosterone, cortisol or DOC. It seems likely that the oestrogenic component plays a significant role, possible by affecting plasma volume and cardiac output, but this remains to be confirmed.

*Acknowledgments*—The authors would like to express their thanks to the staff and patients of the Glasgow Clinic of the Family Planning Association for their co-operation.

## REFERENCES

1. Carmichael S. M., Taylor M. M. and Ayers C. R.: *Obstet. Gynec.* **35** (1970) 371–376.
2. Clezy T. M., Foy B. N., Hodge R. L. and Lumbers E. R.: *Br. Heart J.* **34** (1972) 1238–1243.
3. Spellacy W. N. and Birk S. A.: *Am. J. Obstet. Gynec.* **112** (1972) 912–919.
4. Weir R. J. Briggs E., Mack A. Naismith L., Taylor L. and Wilson E.: *Brit. med. J.* **1** (1974) 533–535.
5. Harris P. W. R.: *Lancet* **ii** (1969) 466–467.
6. Wallace M. R.: *Austral. N.Z. J. Med.* **1** (1971) 49–52.
7. Weir R. J., Tree M. and McElwee G.: Proc. 4th Int. Congr. Endocrinology, (Washington, 1972). Excerpta Med. Int. Congr. ser. **273** (1974) 1019–1025.
8. Weir R. J., Tree M. and Fraser R.: *J. Clin. Path.* **23,** Suppl. 3 (1970) 49–54.
9. Weir R. J., Briggs E., Browning J., Mack A. Naismith L., Taylor L. and Wilson E.: *Lancet* **1** (1971) 467–471.
10. Weir R. J., Tree M., Fraser R. Chinn R. H., Davies D. L. Düsterdieck G. O., Robertson J. I. S., Horne C. H. W. and Mallinson A. C.: Proc. 3rd Int. Congr. Hormonal Steroids. (Hamburg 1970). Excerpta Med. Int. Congr. ser. **219** (1971) 929–937.
11. Brown J. J., Davies D. L., Lever A. F., Robertson J. I. S. and Tree M.: *Biochem. J.* **93** (1964) 594–600.
12. Tree M.: *J. Endocr.* **56** (1973) 159A–171.
13. Dusterdieck G. and McElwee G.: *Eur. J. clin. Invest.* **2** (1971) 32–38.
14. Fraser R. and James V. H. T.: *J. Endocr.* **40** (1968) 59–72.
15. Fraser R., Guest S. and Young J.: *Clin. Sci. Mol. Med.* **45** (1973) 411–415.
16. Wilson A. and Fraser R.: *J. Endocr.* **51** (1971) 557–567.
17. Davies D. L. and Robertson J. W. K.: *Metabolism* **22** (1973) 133–137.
18. Saruta T., Saade G. A. and Kaplan N. M.: *Archs Int. Med.* **126** (1970) 621–626.
19. Crane M. G., Harris J. J. and Winsor W.: *Ann. Int. Med.* **74** (1971) 13–21.
20. Fisch I. R., Freedman S. H. and Myatt A. V.: *J. Am. Med. Assoc.* **222** (1972) 1507–1510.
21. Walters W. A. W. and Lim Y. L.: *J. Obstet. Gynaec. Br. Cwlth.* **77** (1970) 1007–1012.
22. Cain M. D., Walters W. A. and Catt K. J.: *J. clin. Endocr. Metab.* **33** (1971) 671–676.
23. Beckerhoff R., Vetter W., Armbruster H., Luetscher J. A. and Siegenthaler W.: *Lancet* **1** (1973) 1218–1220.
24. Schalekamp M. A., Beevers D. G., Briggs J. D., Brown J. J., Davies D. L., Fraser R., Lebel M., Lever A. F., Medina A., Morton J. J., Robertson J. I. S. and Tree M.: *Am. J. Med.* **55** (1973) 379–390.
25. Tobon H.: *Obstet. Gynaec.* **40** (1972) 681–685.
26. Lehtovirta P.: *J. Obstet. Gynaec. Br. Cwlth.* **81** (1974) 517–525.