Effect of oral contraceptives on blood pressure and on plasma renin, renin substrate, and corticosteroids

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SYNOPSIS A rise in blood pressure associated with oral contraceptives is well established but the frequency with which it develops is not known. Early results from a controlled long-term prospective study have shown no significant change in mean systolic or diastolic pressures or mean weight in 31 women after four months on oral contraceptives. In no individual subject was there a significant change in blood pressure or weight over the short period of the experiment.

In 10 women, oral contraceptives have been shown to induce a consistent rise in plasma renin substrate and cortisol concentrations after four weeks. At this time plasma renin concentration had fallen slightly in eight out of 10 women but neither plasma aldosterone nor plasma corticosterone showed any consistent response.

Raised blood pressure (above 140/90 mm Hg) associated with oral contraceptives has been reported on several occasions but the incidence of hypertension in women taking these drugs is not known. Changes in renin substrate, renin, and aldosterone secretion and excretion have also been observed, but no direct relationship between these factors and the rise in blood pressure has yet been established. This paper is arranged in two sections: a short review of blood pressure and endocrine changes during the administration of oral contraceptives followed by a preliminary report of a study of their effects on the plasma concentrations of renin, renin substrate, aldosterone, corticosterone, and cortisol.

Effect on Blood Pressure

A few single cases of hypertension have occurred in women taking oral contraceptive preparations (Brownrigg, 1962; Owen, 1966) and two reports describe hypertension, malignant in one case, developing during this treatment (Dussek, 1969; Harris, 1969). In 1967, Woods reported blood pressures in excess of 140/90 mm Hg in six

patients within six weeks to two years of starting treatment. Four of these women had previously been normotensive (below 140/90 mm Hg) and, after withdrawal of the contraceptive, blood pressure fell to initial levels in three cases within two months. In two women, essential hypertension was aggravated by oral contraception but subsided to initial levels when this was withdrawn.

Laragh, Sealey, Ledingham, and Newton (1967) also found a relationship between the institution of oral contraceptive therapy and the development or enhancement of high blood pressure in eight hypertensive patients, six of whom were known to have been normotensive before treatment. A similar association in six women was reported by Weinberger, Dowdy, Nokes, and Luetscher (1968).

In a retrospective study of the effects of oral contraceptives on the total population taking these compounds, Loudon and Burton (1969) analysed data of three years from 153 cases, and found a mean annual systolic increment of 1.8 mm Hg and a diastolic increment of 0.7 mm Hg, both greater than would be expected from the effects of aging alone. Goodlin and Waechter (1969), in a retrospective review of 120 randomly

selected women, concluded, however, that no consistent pattern was present over a similar period. A series of 496 contraceptive users were found to have significantly higher mean systolic and diastolic pressure levels than non-users after correction for age, height, weight, and arm circumference, but in a sample after a further year no change in blood pressure was found in either group (Kunin, McCormack, and Abernathy, 1969).

A short prospective study of 43 women with diastolic pressures below 80 mm Hg taking Ovulen (ethynodiol diacetate: 1 mg, mestranol: 0.1 mg) was described by Tyson (1968). Of these, six showed a rise in diastolic pressure to 90 mm Hg or more after one to four months of treatment, which was reversed in all six within 30 days of withdrawal of the drug. No abnormal blood pressure changes were found in 120 women of comparable age, followed simultaneously, using an intrauterine contraceptive device. This contrasts with the work of Chernick (1968) who found no statistically significant difference in the proportions of patients with raised blood pressure between a group of 303 women using Orthonovum (norethindrone: 5 mg, mestranol: 0.075 mg) and another of 56 women using an intrauterine contraceptive device for periods of up to the equivalent of 10 menstrual cycles.

In a larger prospective study over two years of some 9,000 patients taking oral contraceptives (Chiddell, 1969) 90 women had blood pressures over 140/90 mm Hg, 31 of whom had levels below this at their first visit to the clinic and 37 of whom were already taking oral contraceptives when the initial blood pressure readings were taken. Fifty per cent of those whose blood pressure was already high (>140/90 mm Hg) showed a further rise on taking the drug. When the drug was withdrawn, 84% of all the cases with high blood pressure showed an improvement in this measurement, while pressure remained high in 91% of those cases where the treatment was continued.

One possible explanation of the hypertensive effects of oral contraceptive steroids may be an alteration in the activity of the renin-angiotensin-aldosterone system. This is discussed in the next section.

Effects on Plasma Renin, Renin Substrate, Aldosterone, Corticosterone, and Cortisol

Renin released from the juxtaglomerular cells of the kidney reacts with an alpha-2-globulin fraction of plasma ('renin substrate') to form a decapeptide, angiotensin I, which is further split to an active octapeptide, angiotensin II, by a converting enzyme (Fig. 1). Angiotensin II, which will now be referred to as 'angiotensin', may act on peripheral blood vessels as a vasopressor, directly

on the kidney, and on the adrenal cortex to stimulate aldosterone secretion. Techniques now exist to measure some aspect of each of the stages in this system. The term 'renin activity' is commonly used to designate the amount of angiotensin formed by incubation of plasma, *in vitro* under standard conditions, and is a function of both renin concentration and endogenous renin substrate content. Plasma renin concentrations on the other hand, must be measured by incubation of extracted renin with a standard substrate preparation, and is independent of endogenous substrate.

Fig. 1 Formation and destruction of angiotensin in blood.

Oral contraceptive therapy consistently leads to an increase in plasma renin substrate (Helmer and Judson, 1967; Laragh *et al.*, 1967; Newton, Sealey, Ledingham, and Laragh, 1968; Skinner, Lumbers, and Symonds, 1969). The maximum effect develops from four days to two weeks after starting treatment, and substrate concentrations return to normal two to four weeks after stopping the drug. Plasma renin activity is raised in the majority of subjects (Laragh *et al.*, 1967; Weinberger *et al.*, 1968; Crane and Harris, 1969) but plasma concentration of the enzyme is not increased, apparently irrespective of the brand of contraceptive compound used, and may even fall (Skinner *et al.*, 1969).

The stage of the menstrual cycle at which treatment commences appears to have no effect on the degree to which renin substrate increases, but rises in renin activity are most marked when the control samples are taken in the first half of the cycle when renin activity is at its lowest (Skinner *et al.*, 1969).

Increased aldosterone secretion and excretion rate in subjects given oral contraceptives, and increased plasma protein binding of aldosterone have been described (Layne, Meyer, Vaishwanar, and Pincus, 1962; Laragh *et al.*, 1967; Weinberger *et al.*, 1968; Crane and Harris, 1969), although these changes have usually appeared in a minority of cases and have been rapidly reversed on discontinuing treatment. Where such effects have occurred, they have been attributed to the oestrogenic component of the 'pill' (Crane and Harris, 1969).

Plasma cortisol concentration rises during oral contraceptive therapy (Layne *et al*, 1962; Burke, 1969; Damkjaer Nielsen, Binder, and Starup, 1969; O'Connell and Welsh, 1969) largely due to an increase in the level of the protein-bound component of the hormone, but as far as we are aware, plasma corticosterone concentration has not previously been measured in this situation.

There follows a preliminary report of a study set up to assess the frequency and degree of blood pressure elevation in a large group of women taking contraceptive tablets, and to examine some of the endocrine changes occurring in a much smaller group.

Methods

BLOOD PRESSURE

Two brands of oral contraceptive have been chosen: Ovulen as a preparation thought to produce frequent sodium retention, and Norinyl-1 (norethisterone: 1 mg, mestranol: 0.05 mg) as one likely to produce less sodium and water retention. Women wishing to use oral contraception are randomly allocated to one or other of these preparations. Women using a cervical cap or an intrauterine contraceptive device act as controls but are not randomly allocated to these methods. Only women who have not taken oral contraceptives for at least six months before the trial are admitted.

Previous medical history and general examination are conducted by the doctors of the Family Planning Association who also select the method of contraception to be used. The blood pressure and weight are recorded by one doctor who has no knowledge of the women's history, or of the contraceptive technique used. Blood pressure is taken in the sitting position using a standard sphygmomanometer cuff on the same arm at each visit. To reduce observer bias, the sphygmomanometer used is that devised by Rose, Holland, and Crowley (1964). Two readings are taken at an interval of four minutes and the second is taken as the resting blood pressure for the individual. Blood pressure and weight are recorded at the first visit to the clinic before the woman begins to take the contraceptive and at two-monthly intervals thereafter at the same time in the menstrual cycle.

PLASMA RENIN, RENIN SUBSTRATE, AND CORTICOSTEROIDS

Ten women were studied before and between two and six weeks after starting oral contraceptives. Seven took Ovulen and the remainder Norinyl. Blood samples were taken at 8 pm from an antecubital vein with the patient seated. Plasma was separated immediately and stored at -20°C . Plasma renin concentration was measured by the method of Brown, Davies, Lever, Robertson, and

Tree (1964), plasma concentrations of aldosterone, corticosterone, and cortisol by a modification of the double isotope derivative technique of Fraser and James (1968), plasma electrolytes by AutoAnalyzer (Technicon, Ltd), and plasma renin-substrate by the technique of Tree and Weir (1969).

Results

BLOOD PRESSURE

The study began in March 1969 and is therefore only five months old to date.¹ So far 92 women have started oral contraceptives (46 on Ovulen, 46 on Norinyl), of whom 69 have been followed for two months and 31 for four months. Of 36 women started in the control groups (24 with cervical cap, 12 with intrauterine contraceptive device, IUCD), 23 have been studied for two months and 17 for four months.

No significant changes in systolic or diastolic blood pressure or in weight have been found in any of the four groups so far (Figs. 2, 3, 4). It is, however, intended to increase the number of women participating in the trial and to follow the effects of treatment over a period of at least two years. No individual case of raised blood pressure has yet been noted in the controlled series but two other cases referred to the Glasgow Blood Pressure Clinic are worthy of mention.

The first of these, a 22-year-old woman with a blood pressure of 120/80 mm Hg before commencing oral contraception (Ovulen), developed a pressure of 180/100 mm Hg after 20 months of treatment. Six weeks after withdrawal of the drug, her blood pressure had fallen to 135/80 mm Hg. As she was anxious to re-start oral contraception, Norinyl was prescribed and two months later blood pressure remains normal. The second case, a woman of 42 with a previous history of hypertension in her second and third pregnancies and also with a family history of hypertension, complained of tiredness and depression after three months on Norinyl. Blood pressure was then 150/85 mm Hg. Norinyl was replaced by Lyndiol (lynestrenol: 5 mg, mestranol: 0.15 mg) for 10 months by which time blood pressure was 150/90 mm Hg, rising to 170/110 mm Hg at 12 months. The oral contraceptive was withdrawn and blood pressure remained high (180/105 mm Hg) at one month later before subsiding to 140/80 mm Hg after a further month. The patient's electrocardiogram, chest radiograph, intravenous pyelogram, blood urea level, electrolytes, and midstream urine specimen were all normal.

PLASMA RENIN, RENIN SUBSTRATE, AND CORTICOSTEROIDS

Plasma renin substrate was significantly raised

¹September 1969.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 2 Mean systolic blood pressure before and during oral and mechanical contraception.

Fig. 3 Mean diastolic blood pressure before and during oral and mechanical contraception.

Fig. 4 Mean weight before and during oral and mechanical contraception.

Fig. 5 Plasma renin substrate before and during oral contraception.

($P < 0.001$) in all 10 women studied (Fig. 6) with levels up to four times those obtained before treatment. No difference was noted between the effects of the brands used. There was no change detectable in concentration over the period of the menstrual cycle.

Plasma renin concentration fell in eight of the 10 subjects (Fig. 6) but this was not statistically significant by Student's *t* test. Although the mean plasma concentrations of aldosterone and corticosterone were slightly higher after oral contraceptive administration, these changes also did not achieve statistical significance (Fig. 7). Conversely, plasma cortisol concentration increased in every case, the mean plasma cortisol showing a significant increase ($P < 0.01$), but in all cases remained within normal limits (Fig. 8) although in the upper part of these.

Discussion

CHANGES IN RENIN, RENIN SUBSTRATE, AND CORTICOSTEROIDS

These results agree with those of previous workers in that oral contraceptives induce a consistent rise in the plasma concentration of renin substrate (Helmer and Judson, 1967; Laragh *et al*, 1967; Skinner *et al*, 1969) and that plasma renin concentration was unchanged or decreased slightly (Skinner *et al*, 1969). Giving oestrogen has long been known to increase the concentration of various plasma proteins and it is highly probable that it is this component rather than the progestogen which causes changes in plasma renin substrate. Helmer and Griffith (1952) found that plasma renin substrate was increased by oestrogen administration and an increase in aldosterone

Fig. 6.

Fig. 7.

Fig. 6 Plasma renin concentration before and during oral contraception. (It will be noted that two control values were supranormal, ie, > 20 units/l. Both subjects were symptom-free and no explanation of these high values can be given.)

Fig. 7 Plasma steroid concentrations before and during oral contraception. (Duplicate samples from a large normal human plasma pool were used to determine the reproducibility of the technique of assay.)

binding protein (Meyer, Layne, Tait, and Pincus, 1961; Layne *et al*, 1962) and cortisol-binding protein (Sandberg and Slaunwhite, 1959; Daughaday, Holloszy, and Mariz, 1961; Layne *et al*, 1962; Doe, Mellinger, Swaim, and Seal, 1967; Keane, Pearson, and Walker, 1969) have been reported in human subjects after similar treatment. These effects have been attributed to an increased hepatic synthesis induced by the steroid hormone. However, plasma renin substrate may increase in renal insufficiency and after bilateral nephrectomy (Cook and Lee, 1965; Laragh *et al*, 1967) and the possibility of renal involvement in the response of this globulin to oral contraceptives cannot therefore be ignored.

Progesterone may contribute to the increase in substrate (Newton *et al*, 1968), and, as an aldosterone antagonist (Landau, Bergenstal, Lugibihl, and Kascht, 1955; Landau and Lugibihl, 1961), may possibly also provoke an increase in aldosterone secretion in certain circumstances. Progestogens with an alpha substitute at position C-17, however, may have the reverse effect on aldosterone secretion by promoting sodium retention (Landau, Lugibihl, and Dimick, 1958). The progestogens used in this study were of the latter type and the lack of response of plasma aldosterone in this study may have been due to a balance between the stimulating effects of oestrogen and the suppressing effects of the progestogen.

CHANGES IN BLOOD PRESSURE

No evidence has so far been obtained in this study that blood pressure is affected by Ovulen or Norinyl but it must be re-emphasized that the study is of an inadequate duration for any firm conclusions to be drawn. That hypertension may occur during periods of treatment with oral contraceptives seems indisputable but reliable

assessment of its frequency is still lacking, nor is it yet known whether the majority of women taking oral contraceptives experience small increases in blood pressure or whether this is restricted to a small proportion of susceptible women in whom the rise is severe.

The mechanism by which blood pressure is increased is unclear. Changes in plasma renin or renin substrate concentration do not provide an explanation since they appear to occur irrespective of changes in weight and blood pressure. A family or personal history of hypertension, in renal disease or pregnancy, may predispose towards hypertension during oral contraception in some cases (Woods, 1967; Laragh *et al*, 1967), although Chiddell (1969) could not find any correlation between toxæmia in pregnancy and hypertension during oral contraception. Weight gain and fluid retention occur in some cases but were not a feature of the two hypertensive cases reported in this study.

It seems unlikely that the rise in blood pressure is associated with an increase in the sensitivity of vascular smooth muscle to the vasoconstrictor effects of angiotensin since sodium balance is not altered, and neither progesterone (Chesley and Tepper, 1967) nor an oestrogen-progesterone mixture (Woods, 1967) appears to alter the pressor response to angiotensin in rats.

Increased angiotensin levels may, in some circumstances, exert a direct inhibitory effect on renin activity (Genest, De Champlain, Veyrat, Boucher, Tremblay, Strong, Kiow, and Aurele, 1964; Vander and Geelhoed, 1965; Klaus and Heizmann, 1967). An impairment or failure of this feedback, such as has been postulated for subjects who develop hypertension during oral contraception (Newton *et al*, 1968; Skinner *et al*, 1969), could result in a rise in blood pressure. However, there is no direct evidence for such a hypothesis.

Progesterone causes a rise in blood pressure in

rabbits (Horrobin, 1968). It is possible that the progestogen component of the oral contraceptive preparation may contribute to the development of hypertension in women, but this cannot account for the infrequency of such an occurrence.

It is hoped that a long-term study, possibly augmented by an investigation of the separate effects of oestrogens and progestogens, may reveal more clearly the mechanism of blood pressure changes and its relationship, if any, to changes in the renin-angiotensin-aldosterone system.

This study was supported by grants from the Council for the Investigation of Fertility Control, the James McCunn Trust, and the Medical Research Council.

The authors would like to express their thanks to the staff of the Glasgow branch of the Family Planning Association for their advice and cooperation in this study and also to Mrs Eleanor Prentice for her valuable assistance in carrying out the plasma renin extractions.

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