PAPERS AND ORIGINALS

Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30- μ g oestrogen preparations

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Summary and conclusions

Progestogens probably have metabolic effects that may contribute to the increased risk of cardiovascular reactions associated with combined oestrogen-progestogen oral contraceptives. This possibility was investigated by a study of nearly 2000 reports to the Committee on Safety of Medicines from 1964 to 1977. The reports concerned preparations in which norethisterone acetate in doses of 1.0, 2.5, 3.0, or 4.0 mg was combined with 50 μ g of ethinyl-oestradiol and those in which levonorgestrel in doses of 150 or 250 μ g was combined with 30 μ g of ethinyl-oestradiol. Observed and expected numbers of reports were compared, using retail pharmacy purchase figures as a measure of the use of different preparations. There was a significant positive association between the dose of norethisterone acetate and deaths from stroke and ischaemic heart disease (IHD); this association was also found for all cases of these two conditions, fatal plus non-fatal. There were no associations of dose of norethisterone acetate with hypertension or venous thrombosis. The higher dose of levonorgestrel was associated with a possible excess of deaths, non-venous plus venous, and an excess of strokes. There was no association between dose of levonorgestrel and hypertension or venous thrombosis. The reports were also used to assess the relative safety of 30- μ g and 50- μ g oestrogen preparations. Those with 30 μ g of oestrogen were associated with significantly fewer reports of death and IHD (both fatal, and fatal plus non-fatal) than those with 50 μ g of oestrogen. In view of the large-scale move

towards preparations with progressively lower oestrogen doses, there are no grounds for major changes in oral contraceptive practice. Within the range of preparations currently in use, however, there is a case for minimising the dose of progestogen to reduce the chances of thromboembolism.

Introduction

The increased risk of cardiovascular disease in women on combined oral contraceptives is usually attributed to the oestrogenic component. Inman *et al.*¹ using drug safety committee reports for the UK, Sweden, and Denmark, and the Royal College of General Practitioners² (RCGP), have shown dose-response trends that support this view. However, comparisons based on oestrogen dose assume that results are not influenced to any great extent by different progestogens in preparations where the type and dose of oestrogen are the same. Inman *et al.*¹ compared the effects of different progestogens in preparations with the same type and dose of oestrogen. Norethynodrel was associated with a significant deficit of reports in every diagnostic group used—pulmonary embolism, other venous thrombosis, cerebral thrombosis, and coronary thrombosis—while megestrol was associated with a significant excess of reports of venous thromboembolism, but not of cerebral or coronary thrombosis. But no conclusive comparisons could be made between the four preparations containing different doses of the same progestogen, norethisterone acetate, in combination with 50 μ g of ethinyl-oestradiol because the numbers of adverse reaction reports for at least two of these preparations were very small at that time.

In 1977 the RCGP³ suggested a dose-response relationship between norethisterone acetate and hypertension. More recently it has also indicated⁴ a possible effect of norethisterone acetate on superficial venous thrombosis. In another study, Meade *et al.*⁵ suggested that levonorgestrel, the progestogen in 30- μ g ethinyl-oestradiol preparations, may raise blood pressure, though the results were based on only one blood pressure

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reading taken after the women concerned had been on oral contraceptives for varying lengths of time.

To obtain further information on possible progestogenic effects, reports to the Committee on Safety of Medicines (CSM) were analysed for those preparations containing different doses of progestogen at a constant dose of the same oestrogen. Two series of oral contraceptives satisfied these requirements—the norethisterone acetate series, consisting of contraceptives containing norethisterone acetate in doses of 1.0 mg (Minovlar), 2.5 mg (Norlestrin), 3.0 mg (Gynovlar), and 4.0 mg (Anovlar), each combined with 50 µg of ethinylloestradiol; and the levonorgestrel series, consisting of preparations containing 150 µg (Microgynon 30 and Ovranette) and 250 µg (Eugynon 30 and Ovran 30) of levonorgestrel combined with 30 µg of ethinylloestradiol.

Besides comparisons based on progestogen dose, we also compared the reporting of events attributable to the 50-µg and 30-µg oestrogen preparations in the two series, a matter of obvious importance in view of the widespread increase in the use of 30-µg oestrogen preparations since about 1973.

Methods

CSM REPORTS

From January 1964 to December 1977 reports of 2044 suspected cardiovascular and related reactions to the selected oral contraceptives were submitted to the CSM from all parts of the United Kingdom. Of these 44% came from general practitioners, 29% from family planning clinics, 24% from hospitals, and 3% from other sources such as coroners and case reports in journals.

We excluded all reports where oral contraception had been discontinued before the onset of the reaction. Intervals between discontinuation and a reaction ranged from a day to up to several months. We also excluded all reports where the doctor could not give a definite diagnosis and reports that mentioned previous thromboembolic episodes or conditions known to increase the risk of such episodes, such as diabetes mellitus. These and a few other exclusions for miscellaneous reasons accounted for 122 (6%) of the 2044 reactions.

Each reaction was classified as venous or non-venous and as fatal or non-fatal. In view of the findings on hypertension already discussed,^{3,6} non-venous reactions were subdivided into (a) target-organ damage associated with hypertension—that is, ischaemic heart disease (IHD) and stroke; one fatal case of mesenteric artery thrombosis was also included, (b) hypertension itself, and (c) symptoms possibly preceding or associated with the onset of hypertension—weight gain and oedema or headache, with which we included migraine. Sixty-six women had more than one non-venous reaction notified; the commonest combination was of hypertension and headache (13 cases). Each separate reaction was used in the analysis. Venous reactions were nearly all of superficial venous thrombosis or thrombophlebitis, deep vein thrombosis, or pulmonary embolism. Since pulmonary embolism must be preceded by a deep vein thrombosis, we included all notifications of pulmonary embolism with those of deep venous thrombosis in the findings for the latter and we also show findings for pulmonary embolism alone. There were 13 fatal cases of Budd-Chiari syndrome or cerebral or mesenteric vein thrombosis. These were included in the venous deaths and under deep venous thrombosis in the analysis of specific venous events.

In seven cases non-venous and venous reactions were notified for the same woman. For example, four women each had a stroke and a deep vein thrombosis. Each reaction was included in the analysis.

We attributed events and symptoms to the preparation being taken at the time, even if it had been taken for only a few days or weeks and even if other preparations had been taken before the current one. The ages of the women concerned were nearly always given. Of the reports analysed, 77% concerned women aged 20-39, 9% women aged less than 20, and 14% those of 40 and over.

Results are shown for deaths—non-venous, venous, or in total. The fatal events were also included with the larger numbers of non-fatal events in the diagnostic subdivisions. Thus a woman who died of a stroke was included in the group of non-venous deaths and in the stroke subdivision of non-venous events.

Other reactions—We also analysed CSM reports for unintended pregnancies attributed to the failure of the preparations under consideration.

ESTIMATES OF ORAL CONTRACEPTIVE USE

Analyses were based on United Kingdom figures for use of each of the selected preparations, since there is no comprehensive information on the numbers of women on each preparation. For the whole of the relevant period (1964-77) figures were kindly provided by Intercontinental Medical Statistics Ltd (IMS). These data are derived from purchases by retail pharmacists, thus reflecting prescribing by general practitioners but not by family planning clinics. Figures on the latter were kindly provided by Family Planning Sales Ltd up till 1974, when the clinics were integrated into the National Health Service, and since when clinic sales figures have not been available. Clinic prescriptions accounted for about 10-20% of all prescriptions (IMS plus family planning clinics) for different preparations. Time trends in prescriptions from the clinics were similar to those seen in general practice (IMS) prescribing. We therefore used IMS data as they account for most of the prescribing of oral contraceptives and cover the whole of 1964-77. The IMS Medical Data Index shows the proportions of all prescriptions for a particular preparation given to women in the age groups 12-19, 20-39, 40-54, and 55 and over.

The three companies marketing the preparations studied were asked for figures of total sales. All three kindly provided the information they had, but sales figures were not available for all the preparations over the whole of the period. Company sales figures were all higher than IMS figures, as they included clinic as well as retail pharmacy sales, but the two sets of figures agreed well in trends over time for sales of any particular preparation.

STATISTICAL METHODS

During 1964-77 there were wide fluctuations in the annual numbers of reports to the CSM of suspected reactions to oral contraceptives. The generally high number of reports in the late 1960s and early 1970s has since fallen, while the use of oral contraceptives has increased. The effects of these changes on reporting rates are shown in the figure for the norethisterone acetate "ovlar" preparations. (Norlestrin is omitted from the figure in the interests of clarity; it accounted for only a small proportion of reports and use of norethisterone acetate preparations.) To allow for these time trends, we compared observed and expected numbers of reactions by the method used by Inman *et al.*¹ For any type of reaction in an individual year, the expected number of reactions for a particular preparation, *e*,

$$= \frac{n}{N} \times T$$

where *n* is the sales figure for that preparation in that year, *N* is the sales figure of all the preparations in the relevant series (norethisterone acetate or levonorgestrel) in that year, and *T* is the total number of reports of the reaction of the relevant series in that year. The figures for *e* were then added together to give an expected figure, *E*, for the whole period (1964-77 or 1974-7). The observed numbers for individual years were also added to give an observed figure, *O*, for the same period. Preparations in the 50-µg oestrogen norethisterone acetate series were introduced and first reported on in different years. In particular, Minovlar (1 mg norethisterone acetate) was first reported on in 1968—three years after Norlestrin (2.5 mg) and Gynovlar (3.0 mg) and four years after Anovlar (4.0 mg). Minovlar therefore contributed nothing to either the observed or the expected figures for 1964-7. Analyses for the norethisterone acetate series were also performed using only the 1968-77 data; with one exception they gave the same trends as those using the 1964-77 data. Reports for the levonorgestrel series began in 1974.

The ratios of observed to expected (*O:E*) numbers were tested for linear trend⁶ according to progestogen dose. All the expected numbers in the tables were sufficient to justify use of the χ^2 test.

Results

Table I summarises the findings for the norethisterone acetate series. There was a significant positive association between dose and death from non-venous causes (stroke and IHD) but not from venous causes (mainly pulmonary embolism, but also including the fatal cases of Budd-Chiari syndrome and other venous events). There were significant positive associations of dose with stroke and IHD, both fatal and non-fatal combined. Two of the strokes were due to subarachnoid haemorrhage in the 1.0-mg norethisterone acetate series, three in the 3.0-mg series, and five in the 4.0-mg series. Apart from seven cases of angina pectoris only, all the IHD reports

were of myocardial infarction. There were no associations between dose and hypertension, weight gain, or headache. There was also no association for venous thrombosis, superficial or deep, the latter including pulmonary embolism (see Methods). For pulmonary embolism alone, however, there was a significant inverse association—that is, lower O:E ratios with increasing dose. Finally, there was a significant though not entirely consistent inverse association between dose and unintended pregnancy.

TABLE I—Observed:expected ratios for specified events at different doses of norethisterone acetate in preparations containing 50 µg ethinyloestradiol, 1968-77 (observed numbers are shown in parentheses)

		Norethisterone acetate (mg)				χ^2_1
		1.0	2.5	3.0	4.0	
Deaths:	..	0.91 (46)	1.20 (9)	0.95 (61)	1.27 (27)	1.03
Non-venous	..	0.58 (15)	1.49 (6)	1.16 (39)	1.31 (16)	6.60
Venous	..	1.28 (31)	0.86 (3)	0.73 (22)	1.20 (11)	1.60
Non-venous events:						
Stroke	..	0.75 (56)	0.69 (7)	1.12 (97)	1.39 (38)	9.58
IHD	..	0.58 (27)	1.00 (6)	1.30 (67)	1.29 (20)	13.16
Hypertension	..	0.81 (35)	1.41 (8)	1.11 (55)	1.03 (15)	1.82
Weight gain	..	0.81 (20)	0.75 (7)	1.24 (102)	0.60 (19)	0.03
Headache	..	0.88 (41)	1.25 (15)	1.07 (108)	0.90 (38)	0.14
Venous events:						
Superficial venous thrombosis	..	0.96 (36)	1.67 (13)	0.92 (60)	1.06 (30)	0.03
Deep venous thrombosis	..	1.06 (278)	0.84 (31)	1.02 (324)	0.84 (89)	2.37
Pulmonary embolism	..	1.12 (135)	1.04 (16)	1.01 (135)	0.56 (22)	5.78
Pregnancy	..	1.35 (68)	0.19 (1)	0.75 (36)	0.86 (9)	8.66

χ^2_1 values: 3.84, $p < 0.05$; 6.64, $p < 0.01$; 10.83, $p < 0.001$.

IHD = Ischaemic heart disease.

Table II summarises the findings for the levonorgestrel series. There were too few reported deaths to justify analysis by non-venous and venous subdivisions. For all deaths, the difference between the two doses was just significant at a conventional level. At the higher dose there was a significant excess of reports of stroke, but not of hypertension, weight gain, headache, or venous events. We extended the analysis on levonorgestrel to include reports and sales in 1978 and up to the end of June 1979. This gave an O:E ratio for 1974-9 for stroke of 0.54 and 1.38 for the lower and higher levonorgestrel doses respectively, the observed numbers being 12 and 37 ($\chi^2_1 = 8.47$).

TABLE II—Observed:expected ratios for specified events at different doses of levonorgestrel in preparations containing 30 µg ethinyloestradiol 1974-7 (observed numbers are shown in parentheses)

		Levonorgestrel (µg)		χ^2_1
		150	250	
Deaths	..	0.43 (3)	1.43 (13)	3.89
Non-venous events:				
Stroke	..	0.46 (6)	1.37 (26)	6.39
IHD	..	1.40 (7)	0.67 (4)	1.49
Hypertension	..	0.98 (11)	1.02 (15)	0.01
Weight gain	..	0.97 (7)	1.02 (11)	0.01
Headache	..	1.12 (21)	0.91 (24)	0.48
Venous events:				
Superficial venous thrombosis	..	1.16 (5)	0.90 (6)	0.19
Deep venous thrombosis	..	1.10 (61)	0.93 (76)	0.90
Pulmonary embolism	..	1.14 (30)	0.90 (32)	0.86
Pregnancy	..	1.37 (29)	0.71 (19)	5.08

IHD = Ischaemic heart disease.

Table III compares the 30-µg oestrogen-levonorgestrel series with the 50-µg oestrogen-norethisterone acetate series over the period when the former was available (1974-7). There were significantly fewer non-venous deaths associated with the 30-µg series than with the 50-µg series. The difference for venous deaths was in the same direction. In total, there were significantly fewer deaths—non-venous and venous combined—in the 30-µg oestrogen series. There were fewer reports of IHD associated with 30-µg oestrogen preparations than expected but an excess of reports of weight gain and headache. There were no differences in the venous category. Unintended pregnancy was reported more often for 30-µg than for 50-µg oestrogen preparations.

TABLE III—Observed:expected ratios for specified events at different doses of ethinyloestradiol 1974-7 (observed numbers are shown in parentheses)

		Ethinyloestradiol (µg)		χ^2_1
		30	50	
Deaths:	..	0.59 (16)	1.46 (35)	9.58
Non-venous	..	0.53 (7)	1.52 (18)	6.09
Venous	..	0.65 (9)	1.40 (17)	3.67
Non-venous events:				
Stroke	..	0.82 (32)	1.20 (43)	2.64
IHD	..	0.54 (11)	1.48 (29)	8.97
Hypertension	..	1.16 (26)	0.80 (15)	1.31
Weight gain	..	1.56 (18)	0.44 (5)	7.21
Headache	..	1.35 (45)	0.61 (18)	8.54
Venous events:				
Superficial venous thrombosis	..	1.03 (11)	0.97 (11)	0.02
Deep venous thrombosis	..	1.07 (137)	0.94 (133)	1.20
Pulmonary embolism	..	0.94 (62)	1.06 (69)	0.42
Pregnancy	..	1.33 (48)	0.62 (19)	8.38

IHD = Ischaemic heart disease.

Discussion

Results from the norethisterone acetate series suggest an effect of increasing dose on non-venous deaths; all but one of these deaths was due to stroke or IHD. There was a similar pattern for all cases of stroke and IHD, fatal and non-fatal combined. The findings on levonorgestrel also suggest an effect of increasing dose on stroke, though the difference between the doses in the levonorgestrel series was less than twofold. We found no evidence of adverse progestogenic effects on blood pressure or venous thrombosis.

Several potential biases could have produced spurious results. The actual reporting of serious reactions to the CSM may cover only 10% of all reactions, but this need not invalidate the data, provided reporting is unbiased. It seems unlikely that events were reported because they occurred in association with preparations containing high doses of norethisterone acetate or levonorgestrel; until now concern has centered almost entirely on the oestrogen dose. Inman *et al*¹ did not suggest a qualitative or dose-response effect attributable specifically to norethisterone acetate, and there is no reason to believe that their report influenced use or reporting according to the dose of progestogen. The RCGP's report³ was more likely to have had this effect, but it appeared only in 1977.

Another possible source of bias would be a tendency for women at high risk of non-venous events to be put on preparations with a high dose of progestogen. Our data did not permit analyses based on general medical and social features such as parity and smoking habit, but the RCGP³ found no difference in age, parity, social class, cigarette consumption, or duration of use in women on the three norethisterone acetate "ovlar" preparations. The IMS data, however, suggested that the proportion of older users tended to be greater the higher the dose of norethisterone acetate. Mortality from stroke and IHD rises steeply over the age range of those on oral contraceptives, so we analysed the data on reports and oral contraceptive use within the separate age bands of the IMS data. These analyses did not materially alter the results for stroke and IHD in table I. The IMS figures also showed (as expected) that users of 30-µg oestrogen preparations tended to be younger than those on 50-µg oestrogen preparations but this difference is unlikely to explain to any great extent the results in table III. There was very little difference between the age distributions of those on preparations with the two doses of levonorgestrel (table II).

There are three other ways in which the results might have been biased. Firstly, what appears to be a progestogen effect might have been due to the oestrogen. Women on low-progestogen preparations who developed unwanted effects could have been given higher-dose preparations which relieved these symptoms but did not affect an already established oestrogen-induced pathology leading to a later clinical event. There is no evidence for this. Secondly, events attributed to one preparation might have been due to another taken earlier on.

But a similar proportion (about 75%) of reports for the different norethisterone acetate preparations were based on women who had been taking the attributable preparation for at least six months. In the levonorgestrel series about 60% of the reports were on women who had been using the attributable preparation for at least six months. Most of the rest concerned women who had changed from 50- to 30- μ g oestrogen preparations within that time. Therefore there was a greater chance that some reactions we attributed to the 30- μ g oestrogen preparations may have been due to others, particularly those with 50- μ g oestrogen. Thirdly, Minovlar (1.0 mg) introduced a fourfold dose range into the norethisterone acetate series, which otherwise had a range of less than twofold. Minovlar became available in 1968, its name suggesting "low dosage" and perhaps therefore special safety. The figure shows that the association between norethisterone acetate and non-venous events depended heavily on the contribution of Minovlar during the early years of its availability. There is no evidence that Minovlar's name led

Reports per million cycle-packs by year.

to under-reporting, but the possibility exists. Analyses using only the data on the 2.5-mg, 3.0-mg, and 4.0-mg preparations suggested no effect of norethisterone acetate on non-venous or venous events, though they were based on only small differences in norethisterone acetate dose. In addition, Norlestrin (2.5 mg) accounted for only a few reports, and this should be taken into account in interpreting the apparent anomalies due to Norlestrin in some of the trends in table I. Analyses which omit Minovlar thus inevitably depend heavily on Gynovlar (3.0 mg norethisterone acetate) and Anovlar (4.0 mg), which further narrows the dose range. (Any tendency to relative over-reporting of recently introduced preparations will have exaggerated the number of reactions attributed to Minovlar; any effect of norethisterone acetate will consequently have been underestimated.)

To study as many reports as possible we used notifications from family planning clinics and hospitals as well as from general practice. IMS sales figures corresponded directly only with general practice sources, though, for the reasons given earlier, they provide a valid index of use. We performed additional analyses of most of the data using company sales figures, which cover all outlets. These indicated rather stronger associations than those based on IMS figures. Tables I and II may therefore slightly underestimate the non-venous progestogenic effect. One aspect of our results—the difference between non-venous and venous reactions in their relation to progestogen dose—would persist almost regardless of which figures were used. Unless the contrast can be explained by some kind of

bias, this difference in itself provides evidence for a real effect of norethisterone acetate on stroke and IHD, and the findings on stroke in the levonorgestrel series add to the evidence. The contrast could be spurious if, for example, doctors tended to report non-venous reactions to Minovlar relatively less often than venous reactions during the early period of its availability, but there is no evidence of this.

While norethisterone acetate had no effect on superficial or deep venous thrombosis, an increasing dose was associated with fewer reports of pulmonary embolism than would be expected. There are three possible explanations: firstly, the data may be biased; secondly, there might be a real, though unexpected, effect, which would mean that norethisterone acetate reduces the chances of embolisation of a venous thrombus but does not affect the initial development of the thrombus; or thirdly, it may be a chance observation. Because this was the one instance in which data for 1968-77 did not give almost identical findings to data for 1964-7, too much importance should probably not be attached to the observation.

Progestogens seem to alter cholesterol and high density lipoprotein (HDL) cholesterol concentrations in directions which would favour the onset of clinical arterial disease^{7,8}; glucose metabolism may also be influenced in the same direction.⁹ We have already referred to possible progestogenic effects on blood pressure. The CSM data do not confirm these, possibly because hypertension is obviously a much "softer" end-point than stroke and IHD. On balance, we think that the evidence from metabolic studies and from the CSM data points to a probable progestogenic effect on the incidence of stroke and IHD in women on combined oral contraceptives. Since the effects of different doses of oestrogen at a constant dose of progestogen cannot be assessed, the contributions of the two components cannot be directly compared. The associations we have described should perhaps be considered in the context of an oestrogen-progestogen interaction in which the dose of either may determine the chances of an event. Contrary to previous beliefs, progestogens are not metabolised to oestrogens to any biologically significant extent.¹⁰ Some other metabolite, or the progestogen itself, must therefore be responsible for any effects.

In view of the increasing use of low-oestrogen dose preparations the findings in table III are reassuring. Deaths and IHD (non-fatal and fatal combined) were reported significantly less for the 30- μ g preparation than for the 50- μ g oestrogen preparations. The absence of differences for stroke and venous events might be due to relative over-reporting of the more recently introduced 30- μ g oestrogen preparations, since some of the events we have attributed to 30- μ g oestrogen preparations may have been due to those with 50- μ g oestrogen. For these reasons, table III may give a conservative picture of the comparative safety of 30- μ g oestrogen preparations. The excess of reports of weight gain and headache for 30- μ g oestrogen preparations may be another indication of relative over-reporting for this series. Alternatively, it might represent a real effect attributable to levonorgestrel.

We analysed data on unintended pregnancies to test the CSM data for an expected association. They suggested that low doses of both progestogen and oestrogen were associated with increased chances of pregnancy. The relationships provide some support for the validity of the CSM data, but we do not suggest that the relative frequencies of pregnancy by progestogen or oestrogen dose are of any real practical importance. Both 50- μ g and 30- μ g oestrogen preparations carry only small chances of failure—between 0.1 and 0.2 per 100 woman-years. Those figures compare favourably with other methods of contraception, apart from sterilisation (M P Vessey, personal communication).

Our results provide support for the large-scale move towards preparations containing low doses of oestrogen. There are thus no grounds for alarm or for major changes in oral contraceptive practice; comments in professional and lay media should make this clear. Nevertheless, within the range of preparations

currently in use there is a case for minimising the dose of progestogen to reduce the chances of thromboembolism.

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Progesterone, fluid, and electrolytes in premenstrual syndrome

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Summary and conclusions

Changes in mood, plasma progesterone concentration, urinary volume, sodium excretion, sodium:potassium ratio, and body weight during the menstrual cycle were determined in 18 women with premenstrual syndrome and 10 symptomless (control group) women. Plasma progesterone concentration was higher in the women with symptoms during the postovulatory phase of the cycle, and the peak progesterone concentration appeared earlier. The changes in progesterone concentration were accompanied by a natriuresis and diuresis that fell towards preovulatory values in the premenstrual phase. Sodium retention was not confined to any definite period. Mood symptoms occurred after the changes in progesterone and electrolyte concentrations.

Progesterone deficiency is probably not the cause of premenstrual syndrome. Thus treatment with progesterone is probably illogical unless a deficiency is detected. Treatment should be aimed at preventing the natriuretic effect of progesterone in the postovulatory phase and the sodium-retaining and water-retaining effects of aldosterone in the premenstrual phase.

Introduction

The aetiology of the premenstrual syndrome remains undetermined. It has been attributed¹ to vitamin deficiency, hypoglycaemia, antidiuretic hormone, "menotoxin," the renin-angiotensin system, aldosterone, prolactin, and imbalance of ovarian hormones. There is little evidence for any of these hypotheses. A

recent study has shown that a mechanism including aldosterone is unlikely.² Studies on prolactin concentrations have given inconsistent findings,³ and many of the other theories have been inadequately investigated. The theory of progesterone deficiency has been popular for some time,⁴ though the evidence is conflicting. Some studies⁵⁻⁶ have shown lower concentrations of progesterone in patients with the syndrome, while others⁷ have shown lower concentrations in only 30% of patients. Moreover, symptoms appeared to precede the hormonal change. Gillman⁸ produced symptoms by administering progesterone, and many of the "progestagenic complications" associated with oral contraceptives are similar to premenstrual syndrome. We report here the relation between changes in progesterone concentration, fluid and electrolytes, body weight, and mood.

Subjects and methods

We studied the cycles in 28 women (18 with premenstrual syndrome and 10 who were symptomless—the control group). Changes in mood, 24-hour urinary volume, total sodium, sodium:potassium ratio, and plasma progesterone concentration were measured in each of four phases of the cycles. Basal body temperature was measured to determine the time of ovulation. Body weight was measured daily.

Change in mood—Visual analogue scales were used for the following characteristic symptoms: tension, anxiety, bloatedness, sadness, depression, aggression, libido, and lethargy. Volunteers marked the 100-mm line every day according to their mood, and the total for all moods was calculated. The difference between the preovulatory phase mean and premenstrual phase mean gave the premenstrual mood index. Thus a single figure was obtained to reflect these symptoms in each cycle. All subjects had already been defined, symptomatic subjects having a consistently positive premenstrual mood index.

Progesterone concentrations were measured by radioimmunoassay, antiserum raised in rabbits being used against an 11-conjugate coupled to rabbit serum albumin after being extracted with hexane.⁹ Standards were assayed in triplicate and samples in duplicate. Replicate assays on commercial control serum (Ortho diagnostic controls III) gave a mean value of $6.29 \pm \text{SD } 0.736 \text{ nmol/l}$ ($1.8 \pm 0.2 \text{ ng/ml}$) with a coefficient of variation of 11.69% between assays and 9.06% within assays. Blood samples were taken on days 4, 12, 18, and 24 of each cycle.

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