be that D.M.P.A., if anything, increases milk production. And, lately, the *I.P.P.F. Medical Bulletin*[9] stated: "Depoprovera [D.M.P.A.] uniquely among progestational drugs, appears to elevate prolactin levels. This finding is the probable basis of the very strong suspicion that exists that Depoprovera injections increase the quantity of milk when given to lactating women." Since prolactin levels were not measured in any of the studies cited, the statement that they were elevated must have been an inference from the reported increases in milk yield. But there are reports both of increases[10,11] and of decreases (Egypt,[12] Sri Lanka,[13] Bangladesh[14]); and since in all D.M.P.A. studies the most commonly reported menstrual side-effect is increased bleeding and spotting, while rising prolactin levels are associated with post-partum amenorrhœa, the I.P.P.F. statement implies a certainty which the evidence does not justify. This matter must be resolved before D.M.P.A. can be considered as the basis for a nationwide family-planning programme. In Bangladesh lactation is the only way to ensure adequate infant nutrition, and lactating mothers commonly come for family-planning advice.

In the United States, the Food and Drug Administration has withheld approval of D.M.P.A. as a contraception because the drug has produced malignant breast nodules in beagles. In addition, there have been suggestions that long-term use of D.M.P.A. may predispose to cervical carcinoma. Our survey can offer nothing on these matters.

As in previous surveys of D.M.P.A., the clients' main complaint was of menstrual irregularities. Yet we judge that, with careful follow-up, many women can tolerate these. Unfortunately there exists a strong possibility that the drug will be misused. If governments, perhaps under pressure from international agencies, adopt a "speed and numbers" approach to family planning, the result is likely to be havoc. For such reasons, the intrauterine contraceptive device has become unacceptable to the population. If women are not well motivated to use D.M.P.A., educated in its drawbacks, and carefully followed-up, they are likely to drop out; and they, in turn, will tell their neighbours to avoid the "injectable".

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HÆMOSTATIC, LIPID, AND BLOOD-PRESSURE PROFILES OF WOMEN ON ORAL CONTRACEPTIVES CONTAINING 50 μg OR 30 μg ŒSTROGEN

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Summary In 15 women on oral contraceptives containing 30 μg œstrogen, mean values for factors II, VII, and X, fibrinogen, fibrinolytic activity, antithrombin III, cholesterol, and fasting triglycerides were intermediate between values for 63 women on preparations containing 50 μg œstrogen and those for 243 premenopausal women not on oral contraceptives. Mean blood-pressure levels, however, were higher in women on 30 μg than in those on 50 μg preparations. In 28 women on 50 μg preparations containing 3 mg or 4 mg norethisterone, mean values of factor VII, fibrinogen, fibrinolytic activity, cholesterol, fasting triglycerides, and systolic blood-pressure were higher than in 15 women whose preparations contained only 1 mg of norethisterone. A less consistent picture was found in women on 30 μg œstrogen preparations containing either 250 μg (10 women) or 150 μg (5 women) *d*-norgestrel. It is concluded that 30 μg œstrogen preparations probably result in smaller hæmostatic and lipid changes than 50 μg preparations but that they may have a blood-pressure-raising effect attributable to the particular progestagen, *d*-norgestrel, used in 30 μg preparations. The safety of these 30 μg œstrogen preparations may thus depend partly on the balance between these two sets of effects. It is also concluded that norethisterone may have effects similar to those attributed to œstrogens.

Introduction

FOLLOWING a recommendation by the Committee on Safety of Medicines in 1969, oral contraceptives containing 75–100 μg of œstrogen were largely replaced by those containing 50 μg. The Royal College of General Practitioners' study[1] suggested that this change resulted in a drop of about 25% in the incidence of deep-vein thrombosis in women on oral contraceptives. In 1970, Inman et al.,[2] using data collected between 1965 and 1969, reported a positive correlation between œstrogen dosage and thromboembolic episodes. On the other hand, Beral[3] found a strong association between cardiovascular mortality in women and oral-contraceptive usage in 21 countries at a time (1971–72) when preparations containing more than 50 μg were no longer in use in many of the countries, and she pointed out that there is still doubt whether the vascular complications of oral contraceptives are related to œstrogen dose. She did not make a direct comparison of the effects of different doses but regarded the cardiovascular mortality associated with the newer lower dose preparations as "disturbing".

Since 1973, preparations containing 30 μg œstrogen have been increasingly prescribed, and in April, 1977, these were designated as "approved and preferred" by

the Family Planning Association; preparations containing 50 μg were classified as "approved". The Association's medical advisory panel[4] thought that, although there was no epidemiological evidence that preparations containing less than 50 μg of œstrogen were safer than those containing 50 μg, it was a reasonable assumption.

It will probably be several years before epidemiological data on the risks attributable to 30 μg preparations are available. Meanwhile, an alternative though indirect approach is to compare the effects of preparations containing different œstrogen doses on the hæmostatic, biochemical, and other pathways in thrombogenesis.

We also consider here the possible effects of different doses of progestagen—a subject on which there is still considerable uncertainty. Inman et al.[2] suggested that some types of progestagen may be associated with an increased risk of thromboembolism, but Poller et al.[5] found that norethisterone in progestagen-only preparations resulted in a tendency towards "reduced coagulability". Until these uncertainties are resolved, judgement must be reserved on whether observed effects are actually due to œstrogens, progestagens, or both.

Methods

This report is based on the findings at recruitment in 321 White premenopausal women participating in a prospective study of cardiovascular disease.[6] 63 were on oral-contraceptive preparations containing 50 μg œstrogen (54 on ethinylœstradiol, 9 on mestranol), 15 were on preparations containing 30 μg (in all cases ethinylœstradiol), and 243 were not on oral contraceptives. The mean durations of oral-contraceptive use in women on 50 μg and 30 μg preparations were 44·9 and 36·7 months respectively. 4 women on preparations containing more than 50 μg œstrogen or for whom the œstrogen content was unknown have been excluded. Further details, including the laboratory methods, have been given elsewhere,[7] the only modification being that in the measurement of factor-II levels in women on 30 μg œstrogen preparations, the Taipan venom method[8] was used instead of the method of Ware and Seegers.[9] The present report deals only with variables already shown[7] to differ significantly between those using oral contraceptives (all œstrogen doses combined) and those not; as previously, fibrinolytic activity, factor VII, fibrinogen, cholesterol, fasting triglyceride, and blood-pressure levels were measured in all the women (apart from a small number of measurements unavailable for technical reasons). Factor-II, factor-X, and antithrombin-III levels were measured in all 15 women on preparations containing 30 μg œstrogen, but only in randomly selected age-matched samples of those on 50 μg preparations and of those not on oral contraceptives. For factors II and VII and antithrombin III, different batches of standard reference materials had to be used as the study proceeded; conversion factors were derived, and the results are directly comparable with those described previously.[7] For factor X, all the samples from the women in this report were assayed against the same standard, and results are expressed as percentages of this standard; the results are not directly comparable with those in our previous report.[7]

Several different progestagens, and different doses of the same progestagen, are used in oral-contraceptive preparations. Norethisterone is most frequently used in preparations containing 50 μg œstrogen, and results are presented for those containing 1 mg of norethisterone on the one hand (28 women) and 3 or 4 mg on the other (15 women). *d*-Norgestrel is the progestagen in currently available 30 μg œstrogen preparations, and all 15 women on 30 μg œstrogen preparations have been classified according to one of the two norgestrel doses concerned—150 μg (5 women) and 250 μg (10 women). It has thus been possible to study progestagenic effects by comparing findings at the same dose of œstrogen. However, because of the wide range of different types and doses of progestagen, the converse—comparison of different œstrogen doses at the same dose of one progestagen—was not possible.

Because there are significant age effects on several variables in women not on oral contraceptives,[7] values adjusted to age 30 (the mean age of the two groups of women on oral contraceptives) had to be used for factor VII, fibrinogen, cholesterol, triglycerides, and blood-pressure in these women, whose mean age is 37·3 (table I); actual values are also shown. In the 59 women aged 25–34 (mean age 29·5) not on oral contraceptives, actual values are virtually the same as the age-adjusted values shown in table I.

P values, based on unpaired *t* tests (two-tailed), are given for (i) comparisons by œstrogen dosage, (ii) comparison of women

TABLE I—HÆMOSTATIC, BLOOD-LIPID, AND BLOOD-PRESSURE VALUES AND ŒSTROGEN CONTENT OF ORAL CONTRACEPTIVES

Œstrogen dose; mean ages	—	Factor II (N.I.H. units/ml)	Factor VII (%)	Factor X (%)	Fibrinogen (mg/dl)	Fibrinolytic activity*	Antithrombin III (%)	Cholesterol (mmol/l)	Triglycerides (g/l)	Blood-pressure (mm Hg)	
										Systolic	Diastolic
(i) 50 μg; 30.9yr	Mean	319·6	121·1	133·7	289·1	36·6	93·1	5·55	1·06	125·3	75·9
	S.E.	8·61	4·42	5·37	9·38	1·67	1·61	0·16	0·08	1·94	1·40
	No. of observations	20	54	14	54	57	20	52	56	63	63
	P, difference between (i) & (ii)	0·1825	0·0140	0·3038	0·7880	0·7051	0·3587	0·3354	0·0516	0·3160	0·0651
(ii) 30 μg; 30·6yr	Mean	299 ·3	96·6	125·8	283·8	35·2	95·9	5·24	0·74	129·7	81·9
	S.E.	12·94	8·56	5·29	12·05	3·25	2·74	0·24	0·10	3·55	2·87
	No. of observations	15	14	15	14	15	15	15	14	15	15
	P, difference between (ii) & (iii)	0·9288	0·0169	0·0011	0·0290	0·1378	0·1301	0·6106	0·4247	0·0028	0·0003
(iii) Not on oral contraceptives; 37·3 yr	Mean	298·0	83·0	99·5	251·8	29·4	101·1	5·12	0·66	117·5	71·8
	S.E.	8·23	1·36	4·88	3·65	0·98	2·06	0·06	0·02	0·96	0·66
	No. of observations	20 (298·0)	207 (91·4)	13 (99·5)	213 (267·9)	224 (29·4)	20 (101·1)	217 (5·57)	210 (0·77)	243 (125·6)	243 (76·9)

*100/dilute-blood clot-lysis time in hours.
†Values age-adjusted where necessary. (Unadjusted values in parentheses.)

on 30 μg preparations and women not on oral contraceptives, and (iii) comparison of users of high and low progestagen preparations within each of the two œstrogen dose levels.

Results

With the exception only of blood-pressure, the values for the women on 30 μg œstrogen preparations are intermediate between the values for women on 50 μg preparations and those for women not on oral contraceptives (table I). The factor-II value for women on 30 μg preparations is virtually identical to that of women not on oral contraceptives. Mean values of factor-VII, triglyceride and cholesterol levels in women on 30 μg preparations are about midway between those of the two other groups. For factor-X, fibrinogen, fibrinolytic activity, and antithrombin III, values in women on 30 μg preparations are not much different from those in women on 50 μg. On the null hypothesis that there is no difference between 50 μg œstrogen preparations in their effects on the variables shown in table I, a conservative estimate of about 5% can be given for the chance that mean values for eight out of ten results (i.e., all except systolic and diastolic blood-pressure) in women on 30 μg preparations will be intermediate between those for women of 50 μg preparations and women not on oral contraceptives.

Findings by progestagen dosage (table II) are confined to variables measured in all women, since few measurements by progestagen dosage are available for factors II and X and antithrombin III. In the assessment of consistency by progestagen dose, increased (rather than decreased) fibrinolytic activity was taken to be the counterpart of increased levels of factor VII, triglycerides, &c., since this was the finding of our previous study.[7] Among women on 50 μg œstrogen preparations, and with the exception only of diastolic blood-pressure, values in women taking 3 mg or 4 mg norethisterone are all higher than in those taking only 1 mg; on the null hypothesis that progestagen dosage has no effect, a conservative estimate that this finding will occur by chance is also about 5%. A less consistent pattern is seen in comparing the users of 30 μg œstrogen preparations by progestagen dose; factor VII, fibrinolytic activity, cholesterol, and triglycerides are higher in those on 250 μg *d*-norgestrel, but the reverse is seen for fibrinogen and blood-pressure.

Discussion

Because 30 μg œstrogen preparations have come into widespread use comparatively recently, and because recruitment of women into the main prospective study has now virtually ended, the number of women on these preparations who have been studied is limited. Consequently, conventionally significant differences by œstrogen dosage have been demonstrated only for factor VII and, possibly, fasting-triglyceride levels. Apart from blood-pressure, the other differences (e.g., in factor-X levels), though not significant, are in the expected direction and suggest that the hæmostatic and biochemical effects of 30 μg preparations may generally be less than those of 50 μg preparations. Factor VII is the hæmostatic variable which has been most consistently reported as increased by oral contraceptives; if it is directly involved in the thromboembolic complications associated with these preparations, its significantly lower level in women on 30 μg as opposed to 50 μg œstrogen preparations is reassuring, even though it is significantly higher in women on 30 μg preparations than in women not on oral contraceptives at all. 30 μg preparations may also elicit much the same increase in fibrinolytic activity as 50 μg preparations; and this increase may possibly compensate for the increases in factor VII, fibrinogen, &c. associated with oral contraceptives.[7] The women on 50 μg œstrogen preparations were, if anything, heavier

TABLE II—HÆMOSTATIC BLOOD-LIPID, AND BLOOD-PRESSURE VALUES IN RELATION TO PROGESTAGEN CONTENT OF 50 μg AND 30 μg ŒSTROGEN PREPARATIONS

Œstrogen and progestagen dose	—	Factor VII (%)	Fibrinogen (mg/dl)	Fibrinolytic activity*	Cholesterol (mmol/l)	Triglycerides (g/l)	Blood-pressure (mm Hg)	
							Systolic	Diastolic
Œstrogen 50 μg:								
(i) Norethisterone 1 mg	Mean	117·8	280·5	33·7	5·57	1·02	124·5	75·3
	S.E.	6·49	13·31	2·02	0·16	0·07	2·60	1·84
	No. of observations	26	25	27	23	25	28	28
	P, difference between (i) & (ii)	0·0789	0·3101	0·3788	0·6413	0·3290	0·4696	0·9366
(ii) Norethisterone 3 or 4 mg	Mean	138·8	304·8	36·8	5·75	1·22	128·2	75·0
	S.E.	9·14	19·88	2·71	0·45	0·24	4·88	3·44
	No. of observations	11	12	13	12	13	15	15
Œstrogen 30 μg:								
(i) *d*-Norgestrel 150 μg	Mean	92·0	291·1	30·3	4·99	0·74	133·7	87·7
	S.E.	17·44	12·29	4·08	0·32	0·17	4·54	6·50
	No. of observations	5	5	5	5	5	5	5
	P, difference between (i) & (ii)	0·6678	0·6819	0·3084	0·4963	0·9609	0·4725	0·1735
(ii) *d*-Norgestrel 250 μg	Mean	100·0	279·9	37·5	5·36	0·75	127·9	79·1
	S.E.	9·67	17·83	4·37	0·34	0·14	4·84	2·82
	No. of observations	9	9	10	10	9	10	10

*100/dilute-blood clot-lysis time in hours.

Mean values in 20 women on preparations containing 50 μg œstrogen and progestagens other than norethisterone (ethynodiol, 5; lynœstrenol, 7; *d*-norgestrel, 5; megestrol, 3): factor VII, 114·3%; fibrinogen, 289·1 mg/dl; fibrinolytic activity, 41·0; cholesterol, 5·35 mmol/l; triglycerides, 1·01 g/dl; blood-pressure, 125·6 mm Hg (systolic), 77·4 mm Hg (diastolic).

than those on 30 μg preparations; according to the hypothesis of Talwar and Berger[10] this will tend to lead to an underestimate, rather than an exaggeration, of the differences by œstrogen dose. Following the start of oral contraception, most changes in hæmostatic variables seem to reach a maximum in 2 years at most, and probably sooner. It is therefore unlikely that our findings are due to the relatively small difference in duration of oral contraception between women on 50 μg and 30 μg preparations.

The consistency of results according to norethisterone dose in table II suggests that this progestagen may have effects on the variables concerned similar to the effects attributed to œstrogen. Once again, the difference in factor-VII levels is interesting. Some of the metabolic products of norethisterone have œstrogenic activity,[11] so that the apparent progestagenic effects may be partly due to what is, effectively, a further dose of œstrogen. Results analysed according to *d*-norgestrel dose are less consistent than those for norethisterone; this may be due partly to the small numbers involved and partly to the fact that the higher dose of *d*-norgestrel (250 μg) is less than twice the lower dose (150 μg), whereas there is a 3-fold to 4-fold difference in norethisterone doses. Norgestrel is also partly metabolised to œstrogen.

For reasons already given, we were unable to compare the effects of two different œstrogen doses at the same dose of progestagen. The differences between the effects of 50 μg and 30 μg œstrogen preparations shown in table I may thus be due to progestagens as well as to œstrogens; our results as a whole suggest effects due to both. In the case of progestagen (table II), our findings on norethisterone are in contrast to those of Poller et al.,[5] though they are obviously not conclusive. Several of the differences are small, and the detection of possible progestagenic effects depends largely on interpreting the data in terms of their consistency as a whole, rather than in terms of differences reaching convincing levels of statistical significance in individual variables.

The apparently paradoxical blood-pressure results by œstrogen dose (table I) could be due to chance, though the results for diastolic pressure suggest the possibility of a real effect. Vessey et al.[12] found no increase in first-event rates for hypertensive disease in women on oral contraceptives (all formulations) compared with women using other birth-control methods. However, the Royal College of General Practitioners' study produced strong evidence[1,13] of a progestagenic effect of oral contraceptives on the rate of diagnosed hypertension. Because, in the College's first analysis,[1] low-œstrogen preparations tended to have high progestagen contents, rates of diagnosed hypertension by œstrogen level were higher on low-œstrogen formulations. Our findings are similar, though they are based on actual blood-pressure levels rather than on diagnoses of hypertension. The main problem in studying the possible effects of progestagens is how to compare the potency of different compounds. This makes it difficult, for example, to attempt the separation of œstrogenic and progestagenic effects by multiple regression. It is possible[14] that norgestrel is many times more potent in its action on the hypothalamic-pituitary/ovarian axis than is norethisterone. Whether the same is true for blood-pressure is unknown; but if it is, the higher mean blood-pressure in the women in our study on 30 μg preparations, compared with women on 50 μg, could be explained in terms of the particular progestagen in 30 μg preparations, *d*-norgestrel; it seems inherently unlikely that the difference, if real, is due to œstrogen. We routinely ask about past history of diagnosed hypertension: none of the women on oral contraceptives had such a history and, in particular, there is nothing to suggest that women had selectively been placed on 30 μg œstrogen preparations because of known hypertension. Weir et al.[15] found no striking changes in blood-pressure according to progestagen dose, but *d*-norgestrel was not one of the compounds studied.

Thus, 30 μg preparations appear to result in smaller hæmostatic and lipid changes than 50 μg preparations. They may, however, have a blood-pressure-raising effect attributable to the particular progestagen, *d*-norgestrel, in currently available 30 μg œstrogen preparations. The safety of these 30 μg œstrogen preparations may thus depend partly on the balance between their effects on hæmostatic and lipid variables on the one hand and blood-pressure on the other. Further work is necessary, however, and should include measurements of blood-pressure before and after starting oral contraception with low-œstrogen preparations. We also conclude that norethisterone may have effects similar to those attributed to œstrogens.

It should be made clear that while norgestrel is the progestagen in currently available 30 μg œstrogen preparations, norethisterone is the progestagen in the 20 μg and 35 μg œstrogen formulations that are also available. However, none of the women in our study was taking 20 μg or 35 μg œstrogen preparations.

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Addendum

This paper was prepared before the publication in *The Lancet* (Oct. 8, pp. 727, 731) of the mortality results of two prospective studies on oral contraceptives. Statements by the Royal College of General Practitioners and the Royal College of Obstetricians and Gynæcologists (p. 757) and by the Committee on Safety of Medicines (p. 758) which accompanied these reports pointed out that it is not at present possible to assess the findings of the two studies in relation to particular formulations of oral contraceptives.