Oral contraceptives, venous thrombosis, and varicose veins

ROYAL COLLEGE OF GENERAL PRACTITIONERS' ORAL CONTRACEPTION STUDY*

SUMMARY. As part of a continuing major prospective survey of oral contraceptive users, analyses of the frequency of reporting of venous thrombosis have been reassessed and updated. The risk of idiopathic deep and superficial thrombosis in the leg is respectively four and two and a half times greater in oral contraceptive users than non-users. There is no evidence that the risk persists after oral contraceptives have been stopped. In the presence of varicose veins the reporting of superficial thrombosis is substantially increased in Pill users and non-users, and the risk is shown to be dependent upon the severity of the varicosities. Varicose veins have little influence on the development of deep vein thrombosis. No relationship has been found between the oestrogen dose or the progestogen content of the combined oral contraceptives and the occurrence of idiopathic deep vein thrombosis in Pill users. In contrast, superficial venous thrombosis in oral contraceptive users is statistically significantly related to both the oestrogen dose and the progestogen content of the Pill.

Introduction

THE Oral Contraception Study is a continuing prospective survey of total reported morbidity and mortality in a large group of women. The Study began in April 1968, and in the following 14 months 1,400 volunteer general practitioners in the UK recruited for observation 23,000 current oral contraceptive users and a similar number of women matched for age and marital status who had never taken the Pill. In 1974 we published a lengthy interim report which reviewed all our important findings (Royal College of General Practitioners, 1974). These included evidence of an increased risk experienced by oral contraceptive users of developing 'idiopathic' deep and superficial venous thrombosis of the leg. The respective relative risks were 5·66 and 1·48, and these values were similar to the estimates based on previous case-control studies (RCGP, 1967; Vessey and Doll, 1969; Sartwell *et al.*, 1969; Boston Collaborative Drug Surveillance Program, 1973).

At that time it was possible to carry out only a fairly simple computation for the exclusion of the most important pre-existing conditions which might influence the development of venous thrombosis. We later undertook a much more extensive and rigorous analysis, as explained further. The results briefly reported by Kay in 1975 did not materially alter our previous assessment.

In this paper we present further analyses using the same method but including more recent data. We also investigate the extent to which the presence of varicose veins affects the risk of venous thrombosis of the leg in oral contraceptive users and non-users.

Since our data are cumulative, the present results cannot provide independent confirmation of our previous assessments but must be regarded as superseding them.

Method

A detailed description of the design and organization of the Study, with an extensive discussion of the interpretation of the results, were included in our interim report (RCGP, 1974). Briefly, this is a survey which aims to record results of the normal clinical practices of the participating doctors. No special examinations are imposed on the patients in the Study. The diagnoses upon which the analyses are based are those made by the general practitioners using, where appropriate, the full resources of the NHS, including specialist advice and investigation. Women who were recruited as current oral contraceptive users and who have remained

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Table 1. Methods used for the exclusion of conditions that might influence venous thrombosis.

1. Patients entirely excluded

a) Reported to have relevant medical disorders:

	ICD codes (incl)
Malignant or unspecified neoplasms	140- 209 230- 239
Endocrine disorders	2400-2587* 2589-2799
Blood disorders	282- 284 286- 288
Central neurological disorders	320- 344 348- 349
Circulatory disorders	390- 429 440- 448
Liver disorders	570- 573
Chronic renal disorders	580- 584

b) Patients admitted to hospital for medical treatment of any other diseases except cerebrovascular and venous thromboembolic disorders

2. Patients partially excluded

a) Surgical operations	Calendar month of the operation and the following calendar month, and associated events.
b) Pregancy	Calendar month after that in which the last menstrual period before the pregnancy occurred to the calendar month following the end of the pregnancy inclusive, and associated events.

c) Periods of observation and associated events following the first report of a cerebrovascular or venous thromboembolic disease.

Periods of observation (women years)	*Takers*	*Ex-takers*	*Controls*
Total	60,632	35,992	110,065
Excluded	26,150	21,223	62,981
Residual	34,482	14,769	47,084

*Premenstrual disorders are coded to category 2588.

continuously on the Pill are categorized as 'takers'. The group also includes, from the time of change, those women originally recruited as 'controls' who later became oral contraceptive users. Thus, the control results represent the experience of a group of women who have never used the Pill. From the time a taker stops the Pill, she is regarded as an 'ex-taker'. Subsequent experience of the Pill by an ex-taker has been excluded from the present analyses. In summary, the experience of the taker group represents first segment Pill usage during the course of the Study, while the subsequent first segment of non-use forms the ex-taker category.

The contribution of each Study patient to her appropriate contraceptive category is measured in calendar months, and the computer calculations are based on women-months of observation. The tabulations, however, show event rates per thousand women years. The diseases are categorized according to the contraceptive status of the woman at the time the diagnoses were made.

The development of venous thrombosis is commonly influenced by pre-existing conditions. As a result of medical and self-selection the occurrence of these is known to differ between the contraceptive categories. Thus, comparisons can be properly made only if we consider those reported thrombotic events occurring in women without known relevant pre-existing conditions —the so-called 'idiopathic' venous thromboembolic diseases.

The complex computation required for the calculation of idiopathic events is detailed in Table 1. The rates in each of the three contraceptive categories have been standardized by the indirect method for age, parity, cigarette consumption, and social class. The experience of the total residual population has been used as the standard.

Cerebrovascular diseases have also been investigated, but the results will be reported separately.

We have generally used the *International Classification of Diseases* (WHO, 1965) for coding morbidity and mortality. The classification unfortunately fails to distinguish between deep and superficial venous thrombosis in the leg. As before, we have used our own classification for these diseases and this is shown in the tables.

Results

Table 2 shows our main findings. There is a highly significant increased risk of deep and superficial thrombosis of the leg in takers compared with controls. The risk of deep vein thrombosis in current oral contraceptive users is 4·17 times greater than in the non-users, and this estimate is in close conformity with those of other studies. The corresponding relative risk of 2·41 for superficial lesions is similar to the finding in the RCGP case-control study in 1967.

Although the trends are similar, in the two other disease categories (Table 2) the numbers are small and the differences do not reach statistical significance. The number of cases in both these categories is too small to warrant further consideration in this paper.

It is important to note that the rates in ex-takers do not differ materially from those in the controls. This implies that there is no residual effect on venous thrombosis after the Pill has been stopped.

Table 2. Idiopathic venous thrombosis and embolism.

	Takers		Ex-takers		Controls		Ratio of standardized rates	
	Observed number	Standardized rate (TWY)	Observed number	Standardized rate (TWY)	Observed number	Standardized rate (TWY)	Takers/ controls	Ex-takers/ controls
Deep vein thrombosis of leg	30	0.82	2	0.15	9	0.20	4.17* (2.1-10.9)	0.75
Superficial vein thrombosis of leg	67	1.86	12	0.87	36	0.77	2.41* (1.4-2.7)	1.13
Thrombosis of other and unspecified sites	12	0.29	1	0.07	4	0.10	2.94	0.69
Pulmonary embolism	6	0.19	1	0.08	4	0.08	2.39	1.00
Periods of observation (women-years)	34,482		14,769		47,084			

TWY = thousand women years.
*$p < 0.01$.
95% confidence limits of significant rate ratios are shown in parentheses.

Correlations with personal characteristics

The frequency of reporting of idiopathic deep and superficial venous thrombosis of the leg shows no correlation with either cigarette consumption or social class in any of the contraceptive categories. Neither disease rate is correlated with the duration of use of the Pill. For deep lesions there is no correlation with either age or parity. On the other hand, there is a strongly positive relationship between superficial lesions and age (Table 3) and a weaker relationship with parity which is probably age-dependent. All these observations are in agreement with those of other studies (RCGP, 1967; Vessey and Doll, 1969; Sartwell *et al.*, 1969; Boston Collaborative Drug Surveillance Program, 1973).

Correlation with oestrogen and progestogen content

A study of the separate effects of the oestrogen and progestogen components in the combined Pill is fraught with problems (Edgren and Sturtevant, 1976). The two hormones interact and this makes it difficult to establish their potency when in combination. However, we have described previously (RCGP Oral Contraception Study, 1977) a valid technique for measuring the relationship of various diseases with the use of norethisterone acetate when combined with a fixed dose of ethinyl oestradiol. The results of this method when applied to venous thrombosis are shown in Table 4. There is a significant positive correlation with the reporting of superficial lesions, but no evidence of a trend in relation to deep vein thrombosis.

No comparable method is available for assessing oestrogen effects. The best we can do is to aggregate the results for various oral contraceptive preparations into different oestrogen dose ranges. This method ignores the possible differences between ethinyl oestradiol and

Table 3. Superficial vein thrombosis of leg by age.

Age (years)	Takers Observed rates (TWY)	(numbers)	Ex-takers Observed rates (TWY)	(numbers)	Controls Observed rates (TWY)	(numbers)
15-19	0.00	(0)	0.00	(0)	0.00	(0)
20-24	1.72	(17)	0.00	(0)	0.18	(2)
25-29	1.66	(16)	0.72	(3)	0.95	(13)
30-34	2.42	(17)	0.96	(3)	0.55	(6)
35-39	1.84	(8)	2.48	(4)	0.93	(6)
40-44	4.26	(7)	1.26	(1)	2.43	(7)
45 +	5.30	(2)	3.35	(1)	2.24	(2)
All ages	1.94	(67)	0.81	(12)	0.76	(36)
Tests for linear trends of rates	$x^2 = 6.44$ $p < 0.02$		$x^2 = 9.44$ $p < 0.01$		$x^2 = 12.16$ $p < 0.01$	

TWY = thousand women years.

Table 4. Effect of progestogen content on idiopathic venous thrombosis.

		Ethinyloestradiol 50 mcg + norethisterone acetate		
		1 mg	3 mg	4 mg
Deep vein thrombosis of leg	Number	5	7	0
	Rate (TWY)	0.78	0.91	0.00
Superficial vein thrombosis of leg	Number	4	16	3
	Rate (TWY)	0.63	2.09	2.25
Periods of observation (women-years)		6,392	7,663	1,333

TWY = thousand women years.
Test for linear trend of rates: deep thrombosis, not significant; superficial thrombosis $x^2 = 5.34$, $p < 0.05$.

mestranol and, more importantly, their interaction with a wide range of different progestogens. The results are given in Table 5. The number of cases of deep vein thrombosis reported on higher oestrogen dose preparations is small and no significant relationship can be demonstrated. A significant trend is evident, however, in respect of superficial lesions.

Effect of varicose veins

It is generally assumed that the presence of varicose veins predisposes to the development of venous thrombosis in the leg. Varicose veins are so common, however, that if they were regarded as an absolute contra-indication, the number of women eligible to use oral contraceptives would be drastically reduced. Most clinicians will prescribe the Pill unless the varicosities are severe. In order to try and rationalize this practice, we have attempted to measure the risks in current users and non-users. The number of cases in ex-takers is too small to permit useful conclusions, and the data have been omitted from the tables. The rates in Tables 6 and 7 have been standardized, as described earlier, except that women with varicose veins (but without any of the other conditions specified in Table 1) have been included in the reference population.

The presence of varicose veins approximately doubles the risk of deep vein thrombosis in users and non-users, but the confidence limits are wide and the ratio is just statistically significant only in the oral contraceptive users. Predictably the influence of varicose veins on the development of superficial venous thrombosis is much greater. There is a highly significantly increased risk in oral contraceptive users and non-users, but in comparing the two groups of women an apparent paradox appears. Varicose veins appear to have less effect in Pill users than non-users. The likely explanation is that there is biased reporting of varicose veins. Pill users are more likely to have varicose veins detected and reported, and they are likely to be of lesser severity than in the non-users.

To test this hypothesis, and to attempt to measure the phenomenon in users and non-users with more uniform degrees of severity of varicose veins, we have separately calculated the rates in those women reported to have had surgical operations for their varicosities. We must emphasize that events occurring during the operative and postoperative periods have been excluded here as elsewhere. The results show that in this subset of women with more severe varicose veins the risk of superficial thrombosis is further substantially increased in users

Table 5. Idiopathic venous thrombosis by oestrogen dose.

	Up to 50 mcg		75 and 80 mcg		100 and 150 mcg	
	Rate (TWY)	(number)	Rate (TWY)	(number)	Rate (TWY)	(number)
Deep vein thrombosis of leg	0.86	(23)	0.77	(2)	0.90	(4)
Superficial vein thrombosis of leg	1.69	(45)	1.91	(5)	3.16	(14)
Periods of observation (women-years)	26,591		2,613		4,435	

TWY = thousand women years.
Tests of linear trends of rates: deep thrombosis, not significant; superficial thrombosis $x^2 = 4.16$, $p < 0.05$.

Table 6. Effect of varicose veins on reporting of deep thrombosis of leg.

	Takers			Controls		
	Observed numbers	Periods of observation (women years)	Standardized rates (TWY)	Observed numbers	Periods of observation (women years)	Standardized rates (TWY)
Cases in women with varicose veins	9	5,039	1.85 (a)	3	9,455	0.31 (A)
Idiopathic cases	30	34,482	0.84 (b)	9	47,084	0.19 (B)
Ratio of rates		a/b 2.20*			A/B 1.66	

*$p<0.05$.
TWY = thousand women years.

and non-users, and the risk is clearly related to the severity.

Discussion

Among the 1,400 general practitioners who have participated in this Study, there is likely to be some variation in the criteria applied to specific diagnoses. However, since all the participating doctors are reporting upon both oral contraceptive users and non-users, the results in these two groups can be validly compared unless knowledge about the use or non-use of the Pill systematically influences the reporting of the disease by the patient and its diagnosis by the doctor. There are other possible sources of bias that might be inherent in the Study design. In our interim report (RCGP, 1974) we gave extensive consideration to an assessment of these potential biases. We concluded that material diagnostic bias occurred only in respect of those asymptomatic conditions found during the routine examinations of oral contraceptive users. The most important example is hypertension. A patient-reporting bias was evident, however, and this appeared to arise from an increased anxiety experienced by oral contraceptive users about their health and their increased opportunity of reporting ill health to their doctors when they attended regularly for repeat prescriptions for the Pill.

We estimated that bias resulted in the reporting of an average of 20 per cent more episodes of illness in the takers than in the controls. We argued that above average bias would be expected for minor conditions which were frequently never reported to doctors and where the diagnosis was often vague. Examples are headache, loss of libido and, to a lesser extent, depression. On the other hand, serious uncommon conditions which no patient would be likely to ignore we believed would be subject to less than average bias.

Our findings in relation to venous thrombosis must be viewed against this background. We must consider the evidence that leads us to believe that our results reflect an association with the pharmacological properties of oral contraceptives rather than an artefact of the Study design.

Table 7. Effect of varicose veins on reporting of superficial thrombosis of leg.

	Takers			Controls		
	Observed numbers	Periods of observation (women years)	Standardized rates (TWY)	Observed numbers	Periods of observation (women years)	Standardized rates (TWY)
Cases in women having varicose vein operations	8	304	32.63 (a)	10	901	9.53 (A)
Cases in all women with varicose veins	54	5,039	10.63 (b)	72	9,455	7.59 (B)
Idiopathic cases	67	34,482	1.89 (c)	36	47,084	0.77 (C)
Ratio of rates		b/c 5.62* a/c 17.26*			B/C 9.87* A/C 12.38*	

*$p<0.005$.
TWY = thousand women years.

Epidemiological evidence

There is remarkable consistency in the estimate of the size of the risk between the several independent case-control studies and our own observations. The more recent finding of a six-fold risk of thromboembolic disease in Pill users in the Oxford/Family Planning Association prospective study gives more direct confirmation of our own prospective data (Vessey *et al.*, 1976; Vessey, 1978).

While it is highly unlikely that the positive findings in the independent studies have all been subject to the same degree of bias, it is not impossible. We must, therefore, present internal evidence that our observations have not been subject to material bias.

According to the arguments set out earlier, we should expect bias to affect minor conditions more than serious diseases. This view is based upon the conditions prevailing in general practice in the UK. Contrary to these expectations, the rates for the more serious deep vein thrombosis show a greater difference between takers and controls than for the less serious superficial lesions. This suggests that bias is an unlikely explanation of the differences. Hougie and Clarke (1974) believe the opposite to be true, but they argue in the different context of hospital practice in North America.

In 1970, public and professional anxiety about the risks of venous thrombosis in Pill users became widespread. Yet the frequency of reporting of these events in our Study was no greater in this and subsequent years than previously. This strongly suggests that bias had little influence upon the reporting.

We have shown that the rates for superficial venous thrombosis in takers are significantly correlated with the dose of oestrogen and the progestogen content of the oral contraceptive in use at the time of the event. These observations of differences within the taker group are independent of any bias that might arise between takers and controls.

Laboratory evidence

Blood clotting mechanisms are disturbed in a large proportion of oral contraceptive users. Poller (1973) has reviewed the extensive and complex literature. Although these changes imply increased blood coagulability they have not been convincingly demonstrated to correlate with an increased risk of thrombosis.

Alkjaersig and her colleagues (1975) have shown a reasonably high correlation in the detection of thrombus formation in human subjects between the ^{125}I-labelled fibrinogen scanning technique and a non-invasive method of plasma fibrinogen chromatography. Using the latter technique, they undertook serial investigations in a longitudinal study of 154 new oral contraceptive users. Pre-treatment samples from each patient were used as control data. Similarly they carried out cross-sectional studies on over 500 current oral contraceptive users who had been taking the Pill for up to eight years. One hundred and ninety-four non-users attending with minor gynaecological problems were used as controls for this series.

Just over six per cent of the control samples gave positive results, while approximately 27 per cent of each of the treatment series of tests were positive. While the test is certainly not completely accurate in detecting the presence of subclinical thromboses, there is no reason to believe that false results (either negative or positive) would be more or less likely to occur in the treatment than the control tests. Thus, the ratio of positive results can be reasonably assumed to reflect a four to fivefold increased risk of developing silent thrombosis in oral contraceptive users. This risk was found to bear no relationship to duration of use. Women using pills containing 100μG of mestranol had a higher proportion of positive tests than those taking preparations with 50μG of ethinyl oestradiol, but the difference was not statistically significant. The study showed that these commonly occurring silent thrombi normally rapidly resolved without adverse consequences.

Dose-dependent responses

Inman and colleagues (1970), pooling internationally collected data, found a significant relationship between the oestrogen dose and the frequency of reporting of thromboembolic disease. Both Stolley and his colleagues (1975) and our own previously published data (RCGP, 1974) showed similar but non-significant trends. Our present results do not confirm that the incidence of deep vein thrombosis is related to the oestrogen dose, but the small numbers might by chance conceal a trend. With superficial lesions a statistically significant correlation is apparent.

Because of the change of use initiated in 1970, the majority of venous thrombotic events occurring in low oestrogen dose users were reported after that date, while those on higher dose were reported before 1970. However, since there is no correlation of deep vein thrombosis with age, duration of use, nor duration of observation, the secular changes do not confound these oestrogen-dose calculations. On the other hand, superficial lesions are related to age, and this would have the effect of reducing the dose differentials, but not to an important extent.

Because of the interaction with a variety of progestogens the pharmacological implications of these findings are obscure. Our observation of the dose-dependent effect of norethisterone acetate, however, must have a pharmacological basis. It is likely that other progestogens have a similar action, though on theoretical grounds we might expect norgestrel to react differently. We believe that this progestogen response has not been reported before and it requires confirmation.

Effect of varicose veins

Our observations tend to confirm clinical assumptions.

The presence of varicose veins substantially increases the risk of superficial venous thrombosis, and the risk depends upon the severity of the varicosities. Compared with controls without reported varicose veins, oral contraceptive users with varicose veins severe enough to require operation have an excess risk of 32 per thousand users per year. Even this extreme risk of a benign disease might be acceptable, and the risk is much reduced if the varicosities are mild.

It is more difficult to assess the effect on deep vein thrombosis, partly because our low numbers prevent a thorough analysis. Again compared with the unaffected controls the excess risk in oral contraceptive users with varicose veins of varying severity is approximately 165 per hundred thousand users per year, or 1 in 600. Users without reported varicose veins have an excess risk of 1 in 1,500 per year, and those with mild varicosities probably have an intermediate risk—1 in 1,000 is a reasonable guess and is an estimate that most prospective Pill users can readily understand. Whether this risk is acceptable depends on a careful consideration by doctor and patient of all the circumstances in a particular case. We must emphasize, however, that these risk estimates are approximate and our evidence suggests that the presence of varicose veins has little affect on the development of deep vein thrombosis in the leg.

Conclusions

We believe that the association with oral contraceptive usage of an increased risk of deep and superficial thrombosis can no longer be in doubt. In the absence of any other acceptable explanation a causal relationship must be assumed—a relationship which moreover is supported by the laboratory evidence we have cited. The risk can be minimized if the patient has no varicose veins. The observations on oestrogen-dose effects are increasingly difficult to interpret, but it makes good therapeutic sense to use the lowest effective dose. We believe there is now clear evidence that doctors and pharmaceutical companies must give more attention to the clinical effects of the progestogen component.

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Serum digitalis concentration—does it diagnose digitalis toxicity?

We propose that an investigation of the serum digitalis concentration as a test for digitalis toxicity should (1) study patients with similar toxic manifestations, (2) obtain control concentrations from non-toxic patients with symptoms suggesting toxicity, (3) define criteria for toxicity and non-toxicity, (4) select representative patients, (5) describe the study population, and (6) analyse how much diagnostic information the serum digitalis concentration provides that cannot be inferred from other observations. To determine whether available evidence validates the digitalis concentration as a test for toxicity 27 reports were reviewed. No investigation employed symptomatic controls. Of five studies most consistent with points 1 to 5 only three demonstrated higher mean serum digitalis concentrations in toxic patients. Whether knowledge of the digitalis concentrations was diagnostically more useful than knowledge of the digitalis dosage, renal function, serum potassium concentration, and cardiac status, was not determined in any study. The usefulness of the serum digitalis concentration as a test for digitalis toxicity is therefore not established.

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