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Epidemiological and public health aspects of oral contraceptives and thromboembolic disease[1]

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SYNOPSIS The evidence relating oestrogen-progestogen oral contraceptives to venous thrombosis, pulmonary embolism, and cerebral thrombosis is reviewed. The risks associated with the use of oral contraceptives are then discussed in relation to the risks associated with the use of less effective methods of birth control.

The possibility that the use of oral contraceptives might increase the risk of thromboembolic disease was first raised by a case report in the *Lancet* in 1961 (Jordan, 1961). The patient concerned was a 40-year-old nurse who had been given Enavid for the control of endometriosis. After some weeks, the treatment had to be discontinued because of severe vomiting. Ten days later, that is, one week after the vomiting had stopped, the patient developed pulmonary embolism. Since that time many hundreds of similar case histories have been published in the medical journals or reported to national adverse drug reaction committees. The majority of these reports describe deep venous thrombosis of the lower limbs or pulmonary embolism, but others relate to cerebrovascular accidents, coronary thrombosis, mesenteric and other arterial thrombosis, and the Budd-Chiari syndrome.

All these disorders also occur in young women who do not use oral contraceptives and, in themselves, the case reports provide no valid evidence that the preparations are a cause of the diseases in question. For further progress, it is necessary to make estimates of the incidence of the diseases in women using oral contraceptives and to compare them with the incidence in women not doing so. This, of course, was appreciated at once, and between 1962 and 1966 a number of such comparisons were made (Searle & Co., Chicago Conference, 1962; United States Food and Drug Administration 1963, 1966; Cahal, 1965). Each of these comparisons, however, lacked satisfactory control data and depended on the voluntary notification of episodes of thromboembolism by doctors for the calculation of morbidity or mortality rates in users of oral contraceptives. These serious inadequacies inevitably led to inconclusive results and the problem remained unresolved until three controlled investigations were undertaken in the United Kingdom during 1966.

The three British studies were all of the retrospective or case-control type. In one, organized by the Royal College of General Practitioners (1967), 29 family doctors interviewed 147 married women aged 15-49 years who had consulted them for an episode of thromboembolic disease. In a second, Vessey and Doll (1968, 1969) investigated 131 married women aged 16-40 years admitted to one or other of 19 large general hospitals during 1964-67 with thromboembolic disease without evident predisposing cause. In the third, Inman and Vessey (1968) investigated all the 493 deaths that had occurred in England, Wales, and Northern Ireland during 1966 in women aged 20-44 years in which thrombosis or embolism of the pulmonary, cerebral, or coronary vessels

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was mentioned on the death certificate. For comparative purposes, control series of women, matched to correspond with the affected patients in a number of important respects, were investigated in each of the three studies by methods similar to those that had been used for the patients with thromboembolism.

The study carried out by the Royal College of General Practitioners was concerned principally with the common condition, superficial thrombophlebitis, and it indicated that the risk of developing this disorder was increased threefold among women who were using the contraceptives. The principal results of the other two investigations are summarized in Table I. In the absence of any evident predisposing cause, the risk of hospital admission or death from deep vein thrombosis, pulmonary embolism, or cerebral thrombosis was found to be increased six to eight times by the use of the preparations. In contrast, no significant evidence was obtained that oral contraceptives are a cause of coronary thrombosis.

Retrospective studies are subject to many sources of bias and the results shown in Table I should not be accepted uncritically. In particular, they might have been produced if doctors diagnosed thromboembolic disease more readily, or admitted patients to hospital more readily, when they obtained a history of the use of oral contraceptives than when they did not. Two pieces of evidence suggest that this type of bias is unlikely to explain the results. First, if diagnostic bias were a major factor, the association between the use of oral contraceptives and thromboembolism should be strongest in those patients with the least objective evidence of the disease. In fact, the reverse was found to be true. In the investigation of Vessey and Doll, the proportion of patients who were using oral contraceptives rose from 38% of those with an uncertain diagnosis to 68% of those in whom the diagnosis was established. Secondly, the number of admissions to hospital for venous thromboembolism among women using oral contraceptives increased progressively with the increase in the use of oral contraceptives in the general population, and no increase in the admission rate occurred after periods of maximum publicity concerning the thromboembolic hazards of the preparations.

At the time that the three British epidemiological investigations were being planned, a study very similar to the one carried out by Vessey and Doll was being developed, quite independently, in the United States. The findings in this investigation have now been reported (Sartwell, Masi, Arthes, Greene, and Smith, 1969). One hundred and seventy-five women aged 15-44 discharged alive from 43 hospitals after initial attacks of 'idiopathic' thrombophlebitis, pulmonary embolism, or cerebral thrombosis or embolism, were identified, together with 175 carefully matched controls. All subjects were interviewed to provide information concerning their use of oral contraceptives before admission to hospital. From these data, it was estimated that the risk of admission to hospital for superficial thrombophlebitis was increased by the use of oral contraceptives 3·0 times, for deep vein thrombosis or pulmonary embolism 4·4 times, and for cerebral thrombosis 7·0 times. Considering the small numbers of subjects involved both in the British and in the American investigations, the degree of agreement between the findings in the various studies is remarkable.

In addition to the results of these four epidemiological investigations, there is a substantial body of evidence which offers indirect support to the view that oral contraceptives are a cause of thromboembolic disease. In the case of venous thrombosis and pulmonary embolism, this additional evidence may be summarized as follows:

1 At a number of centres, physicians have reviewed their total clinical experience of venous thromboembolism over a period of time. To draw any conclusions from such reviews, it is

Disorder	*Source of Data*	*No. of Women with a Thromboembolic Disorder with a History of Oral Contraceptives*		*No. of Women Studied*		*Relative Risk Users to Non-users*
		Used	*Not Used*	*With Thrombo-embolism*	*Control*	
Deep vein thrombosis or pulmonary embolism	Inpatients	42 (11·5)[2]	42 (72·5)	84	168	6·3 : 1
	Deaths	16 (4·2)	10 (21·8)	26	998	8·3 : 1
Cerebral thrombosis	Inpatients	11 (3·5)	8 (15·5)	19	[3]	6·1 : 1
	Deaths	5 (1·5)	5 (8·5)	10	[3]	5·7 : 1
Coronary thrombosis	Inpatients	2 (2·1)	15 (14·9)	17	[3]	0·9 : 1
	Deaths	18 (11·4)	66 (72·6)	84	[3]	1·7 : 1

Table I. *Use of oral contraceptives by women suffering from thromboembolic disorders without evident predisposing cause*[1]

[1]Data from series of Vessey and Doll (1969) and Inman and Vessey (1968)
[2]Expected numbers in parentheses
[3]As in corresponding control groups for women with deep vein thrombosis or pulmonary embolism

necessary, of course, to assume a knowledge of the general use of oral contraceptives in the population at large. In one of these investigations Hobel and Mishell (1968) studied all 22 female patients aged 15-45 who had had a diagnosis of pulmonary embolism established by radioisotopic lung scanning from December 1964 to August 1967 at Harbor General Hospital, California. Of these 22 patients, three had embolization after a major operation, two after severe trauma, and three in the puerperium. The remaining 14 had pulmonary embolism (with or without venous thrombosis) in the absence of any predisposing cause. Of these, no fewer than 10 had been taking contraceptive steroids. An equally impressive clinical series has been reported from Denmark by Isager and Pedersen (1966). Only one series, that of Johnson and Rosen (1966), has been reported as having a negative result. Close scrutiny of the data shows, however, that only six patients aged 15-39 were identified who had 'idiopathic' thromboembolism and of these one had had a hysterectomy. Of the remaining five, two had been using oral contraceptives.

All these data must, of course, be interpreted with caution not only because of the absence of any control information but also because it is difficult to avoid the suspicion that negative series would have been less likely to be reported than positive ones.

2 Official mortality statistics for venous thromboembolism have been analysed for England and Wales by Vessey and Weatherall (1968) and for the United States by Markush and Seigel (1969) and Seigel and Markush (1969). In both countries there has been a trend in the national death rates in young women compatible with the increase in the use of oral contraceptives and with the estimates of the risks associated with them.

3 Oestrogens, albeit in large doses, have been implicated as a factor in the causation of puerperal thromboembolism when they are used to suppress lactation (Daniel, Campbell, and Turnbull, 1967; Jeffcoate, Miller, Roos, and Tindall, 1968).

4 Oestrogens have been shown to be a cause of thromboembolism, both arterial and venous, when they are administered to elderly men with arterial disease or cancer of the prostate (Schrogie and Solomon, 1967; Bailar, 1967).

5 A large and confused literature has accumulated relating oral contraceptives to changes in circulating levels of various coagulation factors (see Drill, 1966, and Tausk, 1968, for reviews). There is little doubt that some changes, notably increases in factors VII and X, are common, and although the significance of such changes is uncertain, they are at least consistent with the epidemiological findings.

6 Bolton, Hampton, and Mitchell (1968) have described an increase in platelet sensitivity to adenosine diphosphate as determined by the electrophoretic technique in subjects taking oral contraceptives, with a return of platelet behaviour to normal between treatment cycles. These changes in platelet behaviour are similar to those described by the same authors in patients with occlusive vascular disease.

7 Other workers (Danforth, Maralo-Estrella, and Buckingham, 1964; Goodrich and Wood, 1964; Neistadt, Schwartz, and Schwartz, 1966) have demonstrated changes in vessel walls and in venous distensibility and blood flow produced by the administration of oral contraceptives in man and in animals.

Some of the evidence just described is also relevant to the occurrence of cerebral thrombosis, but in this connexion special mention must be made of several impressive but uncontrolled clinical series of ischaemic strokes in young women that have been reported in the literature. Heyman, Arons, Quinn, and Camplong (1969), for example, studied all female patients aged 15-39 years seen at Duke University Hospital, North Carolina, from 1958-68, in whom a diagnosis of cerebral arterial occlusion without evident predisposing cause was made. In the intervals 1958-60, 1961-64, and 1965-68, the numbers of patients seen who were not using oral contraceptives were four, four, and five respectively. The corresponding numbers who were using oral contraceptives were none, three, and seven respectively. Equally striking results have been published by Bickerstaff and Holmes (1967) and by Bergeron and Wood (1969), while Illis, Kocen, McDonald, and Mondkar (1965), Shafey and Scheinberg (1966), and Cole (1967) have all reported comparable findings. Only Jennett and Cross (1967) have reported negative results. All these data must, however, be interpreted with caution, for the reasons that have been stated previously.

Type of Preparation and Duration of Use

None of the epidemiological data available at present indicate that the risk of thromboembolism is any greater early in the course of medication, when it might be expected to be concentrated if the effect was an idiosyncratic reaction in a specially susceptible fraction of the population, nor that it increases with increasing duration of use.

Extensive data are required to make adequate comparisons between the risks associated with different oral contraceptive formulations. Inman and Vessey (1968) and Vessey and Doll (1969) were unable to detect any such differences, but the results of the American study (Sartwell *et al.*, 1969) suggest that sequential formulations are more hazardous than combined ones.

Genetic Factors

A recent investigation (Jick, Slone, Westerholm, Inman, Vessey, Shapiro, Lewis, and Worcester, 1969) has provided strong evidence that the risk of venous thromboembolism in association with the use of oral contraceptives is only about one-third as great among women belonging to blood group O as among those belonging to the other three groups. Comparable data have yet to be obtained for cerebral thrombosis and it cannot be assumed that the same genetic factors affect the risk of this condition which affects the arteries rather than the veins.

Size and Significance of the Risk

Quantitative data that provide an indication of the absolute size of the risk (as opposed to the relative size of the risk) associated with the use of oral contraceptives have been obtained only from the British epidemiological studies and these are shown in Table II. The impact of the risk to life is, perhaps, better understood if it is compared with the risks from other conditions that are better known and, in particular, with the risk that is associated with pregnancy. Some of these risks are summarised in Table III, from which it may be seen, for example, that at ages 20-34 years the annual risk of death from thromboembolism due to the use of oral contraceptives is about one-quarter of the risk of death from a motor accident and about one-twentieth of the risk of death from all attributable causes associated with one pregnancy.

Oral Contraceptives	*Hospital Admissions*	*Fatalities*	
	Ages 16-40	*Ages 20-34*	*Ages 35-44*
Used	50	1·5	3·9
Not used	6	0·2	0·5

Table II *Annual hospital admission and mortality rates for deep vein thrombosis, pulmonary embolism, and cerebral thrombosis per 100,000 previously healthy women by use of oral contraceptives*

Cause of Death	*Age (years)*		*Death Rates*
	20-34	*35-44*	
Motor accidents	4·9	3·9	per 100,000
Cancer	13·7	70·1	women per
All causes	60·1	170·5	year
Puerperal phlebitis, thrombosis, and embolism	1·3	2·3	
Abortion	5·6	10·4	per 100,000
Complications of delivery	7·1	26·5	maternities
Other complications of pregnancy and the puerperium	8·8	18·4	(live + still
All risks of pregnancy, delivery, and the puerperium	22·8	57·6	births)

Table III *Female mortality from various causes (England and Wales, 1966)*

From the public health point of view, however, it must be remembered that oestrogen-progestogen oral contraceptives, especially of the combined type, offer almost complete protection against pregnancy. All other methods are substantially less effective and in assessing the significance of the thromboembolic risks of oral contraception, due consideration must be given to the dangers of unwanted pregnancy.

For comparative purposes, adequate morbidity data are not available, but in regard to mortality, approximate calculations using widely accepted failure rates for alternative methods of birth control suggest that the thromboembolic hazards in women using oral contraceptives may be approximately balanced by the risks associated with unwanted pregnancies in women using the sheath or the diaphragm. The intrauterine device, on the other hand, shows itself in a favourable light in this type of calculation because it provides more effective contraception than the occlusive methods, but its apparent advantage may be offset by the dangers of uterine perforation and sepsis which have yet to be quantified (Scott, 1968).

For the woman who, for any reason, finds oral contraception the only satisfactory method of birth control, the thromboembolic hazards should, therefore, prove acceptable. For the woman who is prepared to attend assiduously to an effective occlusive method, however, the decision may be less simple as it has been shown that among the highly motivated, failure rates well below those that are generally quoted may be obtained by such means (Sagi, Potter, and Westoff, 1962). It should also be remembered that the use of oral contraceptives is known to entail risks other than the thromboembolic ones (Doll and Vessey, 1970) and that our knowledge of the long-term effects of medication is still very incomplete.

Future Work

Each of the four controlled epidemiological studies has provided estimates of the risk of thromboembolism only for women who were previously in good health. It is, however, of considerable importance to know how the risk is affected in patients who have other predisposing conditions and, in particular, in those who have recently undergone surgery. This aspect of the problem may be satisfactorily evaluated by further case-control investigations.

There is also a need to confirm the results of the retrospective investigations by prospective studies of which at least three are now in progress (see Doll and Vessey, 1970). Such studies, however, will be extremely difficult to carry out and

will be subject to many of the sources of bias which could have affected the results of the case-control investigations. It is, in fact, quite possible that they will add little to our existing knowledge of the problem.

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