Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study

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Abstract

***Objective*—To assess the risk of cerebral thromboembolism in women using low dose oral contraceptives.**

***Design*—A retrospective case-control study.**

***Setting*—All Danish medical, neurological, neurosurgical, and gynaecological departments.**

***Subjects*—All 794 women in Denmark aged 15-44 who had suffered a cerebral thromboembolic attack during 1985-9 and 1588 age matched randomly selected controls.**

***Results*—Of 692/1584 case/control questionnaires sent out, 590/1396 (85·3%/88·1%) were returned. Among the cases, 15 refused to participate, 69 had a revised or unreliable diagnosis, 40 had had thromboembolic disease previously, 13 were pregnant, and 152 had a disease predisposing to a cerebral thromboembolic attack. Of the 323 cases without a known predisposition, 320 reported use or non-use of oral contraception. Among the 1396 controls, eight refused to participate, were mentally retarded, or lived abroad; 18 returned an uncompleted questionnaire; 17 had had thromboembolic disease previously; 31 were pregnant; and 130 had a disease predisposing to a cerebral thromboembolic attack. Thus 1198 non-predisposed controls were available, among whom 1197 reported use or non-use of oral contraception.**

Among the 320 cases, 116 (36·3%) were oral contraceptive users at the time of the cerebral thromboembolic attack. By comparison there were 191 users (16·0%) among the 1197 controls, giving a crude odds ratio of 3·0. After multivariate analysis, including confounder control for age, smoking, years of schooling, and trend in use of different types of oral contraceptives during 1985-90, pills containing 50 μg oestrogen were associated with an odds ratio for cerebral thromboembolic attack of 2·9 (95% confidence interval 1·6 to 5·4), those containing 30-40 μg oestrogen an odds ratio of 1·8 (1·1 to 2·9), those containing progestogen only an odds ratio of 0·9 (0·4 to 2·4). The odds ratio did not change with increasing age or with duration of oral contraceptive use. A 50% increased risk of a cerebral thromboembolic attacks among cigarette smokers (after confounder control) was independent of oral contraception status and age.

***Conclusion*—Low dose oral contraceptives are associated with an increased risk of cerebral thromboembolic attack. Combined or sequential pills containing 30-40 μg oestrogen are associated with a one third reduced risk compared with preparations containing 50 μg oestrogen. Progestogen only pills did not increase the risk of a cerebral thromboembolic attack.**

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Introduction

At the end of the 1980s oral contraceptives were being used by more than 60 million women around the world.[1] In assessing the risks and benefits of oral contraception major attention has been given to the risk of cardiovascular diseases—especially cerebral thromboembolic attacks, which include occlusion of precerebral arteries (ICD (eighth revision) code 432), cerebral thrombosis (ICD code 433), cerebral embolism (ICD code 434), transient cerebral ischaemic attack (ICD code 435), and the unspecified group cerebral apoplexy (ICD code 436), of which 80-90% have been found to be thrombotic.[2-4]

During the past two decades at least 14 retrospective studies have been concerned specifically with the influence of oral contraceptives on the risk of cerebral thromboembolic attacks (table I).[5-18] Among the prospective cohort studies, only two included enough cases for calculating relative risks specifically for cerebral thromboembolism.[19-21]

Although these studies generally reported significantly increased relative risks (or odds ratios) for cerebral thromboembolic attacks among users of oral contraceptives, nine of the 14 retrospective studies and both of the prospective studies were conducted during a period when high dose pills were widely used. The figures from these studies, therefore, do not necessarily apply to the pills used today. It is remarkable that all five retrospective studies published in the 1980s and 1990s found relative risks among users of oral contraceptives of between 3·7 and 4·8.[14-18] However, during the past 10 years the oestrogen content as well as the progestogen content of the pills has been further reduced. In Denmark all oral contraceptive compounds containing more than 50 μg oestrogen ("high oestrogen" pills) were withdrawn in 1974. Since then there has been a change in the distribution of preparations sold containing 50 μg oestrogen ("middle oestrogen" pills), 30-40 μg oestrogen ("minioestrogen" pills—among which are the sequential preparations), 20 μg oestrogen ("micro-oestrogen" pills), and progestogen only pills (see figure 1). Generally, the reduction in the progestogen content has followed the reduction in oestrogen, so that typically middle oestrogen pills contain 250 μg levonorgestrel or more than 1 mg norethisterone, and minioestrogen and micro-

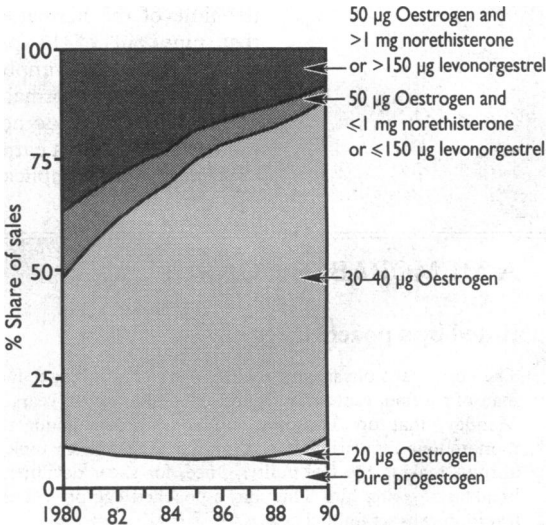

FIG 1—*Changes in oestrogen and progestogen contents of oral contraceptives purchased during 1980-90*

TABLE I—*Retrospective case-control studies and prospective cohort studies specifically concerned with relation between use of oral contraceptives and cerebral thromboembolic risk, and studies either secondarily concerned with influence of oral contraceptives or not indicating odds ratios but from which odds ratios could be calculated*

Reference	Nationality	Period of data sampling	No of cases/ No of controls	Odds ratio (relative risk)	p Value	Age matching	Discrepancy between haemorrhagic and thrombotic diseases	Exclusion of predisposed women	Exclusion of pregnant women
				Retrospective studies					
Inman and Vessey[3]*	UK	1966	10/998	5·6‖	<0·01	+	+	+	+
Vessey and Doll[6]*	UK	1964-6	9/116	13·3‖	<0·001	–	+	+	+
Vessey and Doll[7]*	UK	1964-7	19/168	6·1‖	<0·001	–	+	+	+
Sartwell[8]*	US	1964-8	13/13	19·2‖	<0·005	+	+	+	+
Collaborative Group for Study of Stroke in Young Women[9]*	US	1969-71	98/98	7·2	<0·001	+	+	–	+
Fogelholm and Aho[10]‡	Finland	1966-71	52/RP	(3·7¶)	<0·001	–	+	–	–
Firnhaber and Fügemann[11]§	Germany	1963-70	14/100	1·0‖	NS	–	+	–	–
Hillbom and Kaste[12]‡	Finland	1968-77	39/RP	(5·5¶)	<0·001	–	+	–	–
Jick *et al*[13]*	US	1969-?	14/56	25·7‖	<0·001	+	–	+	+
Lidegaard[14]*	Denmark	1975-81	82/RP	(4·8‖)	<0·0001	–	+	+	+
Hart and Miller[15]†	US	?	19/RP	(4·4¶)	<0·005	–	+	+	+
Mettinger *et al*[16]§	Sweden	1973-7	32/297	4·5¶	<0·001	–	+	–	–
Oleckno[17]§	US	1975-83	25/469	3·7¶	<0·001	–	–	+	–
Thorogood *et al*[18]*	UK	1986-8	21/38	4·4‖	?	+	+	+	+
Present study*	Denmark	1985-9	49/1370	3·0**	<0·001	+	+	+	+
				Prospective studies					
Layde *et al*[4]†	UK	1968-79	81/0	(4-14)	<0·05	+	+		
Vessey *et al*[20]†	UK	1968-84	31/0	(3-4)	<0·01	+	+		

*Case-control study specifically concerned with relation between use of oral contraceptives and cerebral thrombembolic risk.
†Cohort study specifically concerned with relation between use of oral contraceptives and cerebral thromboembolic risk.
‡Study secondarily concerned with influence of oral contraceptives.
§Odds ratio not stated but calculated from data given.
‖Primarily calculated odds ratio.
¶Secondarily estimated odds ratio.
**Crude odds ratio: users *v* non-users of oral contraceptives for comparability with figures in previously conducted studies.
RP=Reference population. In studies marked RP risk calculation was based on sale statistics in reference population. In these cases estimated risks are relative ratios and not odds ratios.

oestrogen pills contain 150 μg levonorgestrel or 1 mg norethisterone or less. Finally, new progestogens have recently been introduced.

Urgent questions are, therefore, do oral contraceptives of the 1990s carry an increased risk of a cerebral thromboembolic attack? And do the differences in hormonal contents of the pills play a part in that risk? This study aimed at exploring these questions.

Subjects and methods

CASES

In Denmark since 1977 the diagnoses of all hospitalised patients have been recorded in the National Patient Register. All women aged 15-44 who suffered one or more of the disorders coded by the ICD as 432, 433, 434, 435, and 436 during 1985-9 were identified from this database. If a woman had experienced more than one cerebral thromboembolic attack during the five years the diagnosis at first discharge from a neurological department was used. This was because women typically are primarily referred to a medical department and only secondarily referred to central neurological departments with computed tomography and other facilities. The included women reported use/non-use of oral contraceptives according to their primary admission. Of 794 women so identified, 782 had a known address in Denmark, the rest being dead or resident abroad. According to the National Patient Register 36 had also suffered a cerebral thromboembolic attack during 1980-4, and these were therefore primarily excluded. We approached the head of each of the 112 departments concerned for permission to send a questionnaire to each of the remaining 746 women, and written permission was obtained for 692. The rest were accounted for as wrong diagnosis (n=20) and no permission (34). Patients for whom permission was not given were mainly those with transient cerebral ischaemia, who were not informed about the possibility of thromboembolism but typically were said to have had a vascular spasm. Questionnaires were sent to most of the 692 women in October 1990, the remaining few being sent in February 1991.

The questionnaire was returned by 590 women (85·3%) (see table II). Information included date of the cerebral thromboembolic attack (also recorded in the National Patient Register); use of oral contraception at the time of the attack; duration of oral contraceptive use; specific brand used; previous use of oral contraception; smoking habit; past history of thromboembolic disease; whether pregnant at the time of the attack; history of other diseases, including treated hypertension, diabetes, and migraine; years of schooling; and whether computed tomography had been performed. Of the 590 women who responded, 93 were secondarily excluded. Nine had suffered a cerebral thromboembolic attack before 1980, 15 refused to participate, 44 had a revised diagnosis (primarily multiple sclerosis or migraine), and 25 had an unreliable diagnosis—that is, the patient denied having had a cerebral thromboembolic attack or the year she stated for the attack was more than one year after the year recorded in the National Patient Register. Thus 497 (84%) respondents had a reliable diagnosis of cerebral thromboembolic attack.

CONTROLS

For each case two controls were selected at random from among women on the National Person Register (which includes all Danish people) matched for day and month of birth with the case but whose current age corresponded with the age of the case at the time of the cerebral thromboembolic attack. Of the 1588 controls, four had no known address. Questionnaires were therefore sent to the remaining 1584 (October 1990), 1396 (88·1%) of whom replied (see table II). Of these, two were unable to participate (mentally retarded), two refused to participate, four were resident abroad, and 18 failed to complete the questionnaires. A total of 1370 completed questionnaires were therefore available. Fifty six women had hypertension, 62 migraine, 12 another predisposing medical disease, 17 a history of thromboembolic disease, and 31 were pregnant. Six women had more than one of these conditions, so that a total of 172 controls were excluded from the oral contraceptive analysis. Among 1198 questionnaires included (76% of the questionnaires

sent out), all but one gave information on use or non-use of oral contraceptives, and 166 (87%) of 191 users could specify the brand.

Information about total sales of different brands of oral contraceptives in Denmark during 1985-90 was obtained from the Danish Drug Statistics.

CATEGORISATION OF USERS OF ORAL CONTRACEPTIVES

Users of oral contraceptives were categorised initially into four groups according to the oestrogen content of the pills—that is, 50 μg (middle oestrogen), 30-40 μg (minioestrogen, including sequential brands), 20 μg (micro-oestrogen), and progestogen only (minipills). There were no users of 20 μg oestrogen pills among the cases, but there were six among the controls. These six controls were therefore included in the 30-40 μg control group. Non-users were categorised as never users and former users.

STATISTICS

The data were analysed by graphical log linear models for multidimensional contingency tables.[22-24] Years of schooling, cigarette smoking, and various medical diseases were all of confounding significance for the relation between oral contraception and cerebral thromboembolic attack. Both marginal (crude) and partial (after correction for one or more variables) test statistics were calculated in order to determine conditional and non-conditional dependence and independence. Significance was tested by both the χ^2 and, in the case of ordinal variables, partial Goodman-Kruskal γ tests.

Risk estimates were calculated as odds ratios with 95% confidence intervals and as the proportion of incident cases for which oral contraceptives were theoretically responsible (the aetiological fraction).

As the controls stated their specific use of oral contraceptives in 1990 and the cases their specific use between 1985 and 1990 the calculation of odds ratios for different types of pills (that is, according to oestrogen content) was adjusted for the time trend in the distribution between pills with different hormonal content during the study period.

The appendix shows the recursive graphical model used in the study.

TABLE II—*Included and excluded cases and controls and their respective use of oral contraceptives*

	No (%)	% Use of oral contraceptives (n)
Cases		
Submitted questionnaires	692	
Returned questionnaires	590 (85·3)	
Refusals	15	
Earlier cerebral thromboembolic attack (before 1980)	9	
Wrong diagnosis*	44	
Unreliable diagnosis†	25	
Reliable diagnoses	497	32·6 (161/494)
Confounder control	174	
Previous thromboembolic disease	31	16·1 (5/31)
Pregnancy	13	—
Predisposition‡:		
Hypertension§ (treated)	68	26·5 (18/68)
Migraine (more than once a month)	49	30·6 (15/49)
Other conditions‖	35	28·6 (10/35)
Non-predisposed women with cerebral thromboembolic attacks¶	323	36·3 (116/320)
Occlusion of precerebral artery (ICD 432)	10	30·0 (3/10)
Cerebral thrombosis (ICD 433)	114	38·9 (44/113)
Cerebral embolism (ICD 434)	15	53·3 (8/15)
Transient cerebral ischaemia (ICD 435)	86	30·2 (26/86)
Cerebral haemorrhage (ICD 436)	98	36·5 (35/96)
Controls		
Submitted questionnaires	1584	
Returned questionnaires	1396 (88·1)	
Refusals, moved, retarded	8	
Uncompleted questionnaires	18	
Completed questionnaires	1370	15·2 (208/1369)
Confounder control	172	
Previous thromboembolic disease	17	5·9 (1/17)
Pregnancy	31	—
Predisposition‡:		
Hypertension (treated)	56	7·1 (4/56)
Migraine (more than once a month)	62	17·7 (11/62)
Other conditions‖	12	8·3 (1/12)
Non-predisposed controls¶	1198	16·0 (191/1197)

*Multiple sclerosis, migraine, brain tumour.
†If patient denied having had a cerebral thromboembolic attack or stated that it occurred more than one year after the time recorded in the National Patient Register.
‡As far as predisposition was expected to influence the use of oral contraceptives. Including 15 with migraine.
‖Cases/controls: connective tissue disease 11/8, coagulopathy 2/0, hyperlipidaemia 4/0, tetraplegia 1/0, psychosis 2/1, severe brain damage 2/1, brain abscess 1/0, heart disease 12/1, brain aneurysm 0/1.
¶"Non-predisposed" refers to women free of confounding predisposing diseases.

Results

ORAL CONTRACEPTIVES AND CEREBRAL THROMBOEMBOLIC ATTACK

Women predisposed to a cerebral thromboembolic attack are usually dissuaded from taking oral contraceptives. Therefore, in analysing the influence of oral contraception on the risk of this condition we excluded cases and controls with hypertension, migraine (more than once a month), hyperlipidaemia, coagulopathies, brain tumours, and cerebral abscess (table II). Among the 497 reliable cases, 152 had a disease predisposing them to cerebral thromboembolic attack. Thirteen pregnant women and 31 women with a past history of thromboembolism were also excluded. Twenty two women had more than one predisposing condition, so that a total of 174 cases were tertiarily excluded from the analysis. The use of oral contraception among these excluded women is shown in table II. Three of the remaining 323 women gave no information on use of oral contraceptives. Among the 320 women for whom this information was available, 116 (36·3%) had been using oral contraceptives at the time of their attack; 109 of these women could specify the brand. Among 1197 non-predisposed controls, 191 (16·0%) were users of oral contraceptives. The corresponding crude odds ratio of developing cerebral thromboembolism among users compared with non-users of oral contraceptives was therefore 3·0 (95% confidence interval 2·3 to 3·9). The odds ratio for any of the five subdiagnoses of cerebral thromboembolic attack did not differ significantly from this overall average.

Among the 204 cases and 1006 controls who were non-users of oral contraceptives, 130 and 800 respectively were former users, 56 and 181 were never users, and 18 and 25 did not specify. Among the 109 cases and 166 controls who specified the brand of oral contraceptive that they had been using, 39 and 23, 63 and 125, and seven and 18 respectively had used pills containing 50 μg oestrogen, 30-40 μg oestrogen, and progestogen only. Thus 295 cases and 1147 controls were included in the multivariate analysis.

The use of oral contraceptives among the controls was assessed in 1990 whereas the use among cases was recorded at some point during 1985-9. Though the trend in total sales of oral contraceptives during 1985-90 showed a small decrease (less than 1%), sales of minioestrogen (30-40 μg) and micro-oestrogen (20 μg) pills increased (fig 1). Odds ratios for having a cerebral thromboembolic attack associated with the various pills as compared with the risk among never users were calculated after adjusting for this time trend and after corrective confounder control for age, smoking, and years of schooling. The results showed that use of oral contraceptives containing 50 μg oestrogen was associated with an odds ratio of 2·9 (95% confidence interval 1·6 to 5·4), use of preparations containing 30-40 μg oestrogen (including the sequen-

TABLE III—*Cerebral thromboembolic risk among fertile women according to hormonal content of oral contraceptives (controlled for age, smoking, and years of schooling) and smoking habits (controlled for oral contraception, age, and years of schooling)*

	Odds ratio	95% Confidence interval
Never users of oral contraceptives	1·0	—
Former users of oral contraceptives (compared with never users)	0·5	0·4 to 0·7
Present users (compared with never users):		
Minipills	0·9	0·4 to 2·4
30-40 μg Oestrogen pills*	1·8	1·1 to 2·9
50 μg Oestrogen pills†	2·9	1·6 to 5·4
Never smokers	1·0	—
Former smokers (compared with never users)	0·6	0·4 to 0·9
Smokers (compared with never users):		
≤ 10 Cigarettes/day	1·6	1·1 to 2·4
> 10 Cigarettes/day	1·5	1·1 to 2·0

Combined risks (never smokers, never users of oral contraceptives, odds ratio=1): *odds ratio with ≤ 10 cigarettes/day 2·9, > 10 cigarettes/day 2·7; †odds ratio with ≤ 10 cigarettes/day 4·7, > 10 cigarettes/day 4·3.

tial brands) an odds ratio of 1·8 (1·1 to 2·9; Goodman-Kruskal test: $p<0·001$), and use of progestogen only pills an odds ratio of 0·9 (0·4 to 2·4; NS) (table III). Adjustment for age was necessary because the exclusion of predisposed women in the case and control populations implied minor age differences between the cases and controls. There was no significant change in odds ratio among users of oral contraceptives with increasing age, and duration of use of oral contraceptives did not influence the risk significantly. Compared with never users of oral contraceptives former users had an odds ratio for a cerebral thromboembolic attack of 0·5 (0·4 to 0·7; χ^2 test: $p<0·001$). Therefore, the risk among users of oral contraceptives compared with non-users (never users plus former users) was about 50% higher (odds ratio=3·46) than the odds ratios with never users as reference. On the other hand, the decreased risk among former users implied that the odds ratio for risk of a cerebral thromboembolic attack among ever users of oral contraceptives (former users plus present users) was smaller than the calculated odds ratios based solely on present users. As only a very small proportion of women have a cerebral thromboembolic attack the calculated odds ratios approximate to the relative risk of such an attack.

SMOKING

Altogether 63·6% of the cases (204/321) and 48·8% of the controls (580/1189) smoked cigarettes. There was no difference in the proportion of smokers between users and non-users of oral contraceptives. After adjustment for age, use of oral contraceptives, and years of schooling smoking was associated with an odds ratio for risk of a cerebral thromboembolic attack of 1·5-1·6 (95% confidence interval 1·1 to 2·4; $p<0·001$) (table III). This odds ratio was independent of age and use or non-use of oral contraception. As no major change occurred in the proportion of cigarette smokers between 1987 and 1990 the calculated odds ratios did not seem to be influenced substantially by any time trend.

During the 1960s and 1970s, when most of the women in this study were of school age, the proportion of women who acquired 13 years of schooling increased dramatically from 6% to 15% and from 15% to 35% respectively. As we had no data with which to correct for this cohort trend exact estimates of the influence of education on the risk of cerebral thromboembolic attack were not possible.

Discussion

In evaluating these results two major questions must be considered: is the documented statistical correlation between oral contraception and cerebral thromboembolic attack valid? And is this correlation a token of a causal relation?

VALIDITY OF DIAGNOSES

We checked the validity of the diagnoses included in the final analysis in three ways and believe that in most cases they represented true cerebral thromboembolic attack. Firstly, all the cases were identified in the National Patient Register, which records doctors' diagnoses at discharge from relevant departments, and in 90·3% of cases (449/497) a computed tomography scan had been performed. The remaining cases were primarily women with transient cerebral ischaemia. Secondly, we approached the head of each department in which a case had been treated for permission to send the woman a questionnaire. When later investigations or the clinical course resulted in a revised primary diagnosis in any case, information could be given to the project group and the case excluded from the study. Thirdly, each woman included in the analysis confirmed her own diagnosis.

VALIDITY OF ORAL CONTRACEPTIVE USE

Women generally recall their contraceptive habits fairly accurately,[25-28] and most of the cases were asked about use of oral contraceptives at the time of their admission to hospital. A woman with a cerebral attack who takes oral contraceptives will almost certainly consider these as a possible cause. Both cases and controls were submitted a list of available brands of oral contraceptives with the questionnaire. Only three women did not answer the question on oral contraception at the time of the attack, and among the 320 responders only seven (6%) of 116 users of oral contraceptives could not specify the brand. Among the controls actual use or non-use of oral contraceptives was stated, so that recall bias was not an issue; only one woman did not specify use or non-use of oral contraception.

SELECTION AMONG CASES AND CONTROLS

Non-responders are important in retrospective case-control studies. Available information on non-responders in this series suggested that their age and geographical distribution were similar to those of the responders and their subdiagnoses no different from those of the included cases. The high response rate among cases and controls implies that response selection alone cannot be responsible for the associations found, although minor influences cannot be excluded. Moreover, the ratio of excluded predisposed cases to excluded controls who were users of oral contraceptives was generally higher than the ratio of included cases to controls who were users. Hence the estimated odds ratios would have been higher had the predisposed women not been excluded. The documented association between oral contraceptive use and cerebral thromboembolic attacks cannot therefore be a consequence of the exclusion of the predisposed patients.

Could women taking oral contraceptives be more aware of any thrombotic symptoms and therefore be overrepresented in the case group, thus being partly responsible for the statistical association between oral contraceptive use and cerebral thromboembolic attack? If this were so we should expect this "surveillance phenomenon" to be particularly pronounced among women with transient cerebral ischaemia, as women with severe neurological symptoms which last more than 24 hours are almost invariably referred to hospital. As the odds ratio for transient cerebral ischaemia was identical with the odds ratios for the four other diagnoses included in cerebral thromboembolic attacks such a surveillance phenomenon does not seem to have any appreciable role.

In conclusion, we have no reason to assume that there was any substantial validity or selection bias concerning either the diagnoses or the use of oral contraceptives. The stated statistical associations between oral contraceptive use and cerebral thromboembolic attacks thus seem to be real.

ORAL CONTRACEPTIVES AND CEREBRAL THROMBOEMBOLIC ATTACK

Despite the fact that nearly all studies on the risk of cerebral thromboembolic attacks among users of oral contraceptives have detected a significantly increased risk, three main concerns question a causal relation.[29-31] Firstly, major methodological problems are attached to the studies, including lack of age matching or control for age, lack of discrimination between haemorrhagic and thromboembolic attacks, and inclusion of predisposed or pregnant women among cases or controls. Secondly, the incidence of cerebral thromboembolic attack among fertile women has not been found to exceed that among age matched men, which it would be expected to if oral contraception implied a substantially increased risk of cerebral thromboembolic attack. Thirdly, the incidence of and mortality from cerebral thromboembolic attacks among fertile women have not increased since the introduction of oral contraceptives. Each of these circumstances may be analysed separately.

METHODOLOGICAL PROBLEMS IN OTHER STUDIES

The small numbers of cases in previous studies implied difficulty in performing different kinds of confounder control (table I). It was this lack of control in most of the studies that led many observers to reject as unacceptable their statistical findings for an association between oral contraceptive use and cerebral thromboembolic attacks.[29-31] Interestingly, however, all the methodological main points which were noted to be lacking tended to underestimate rather than overestimate any such association. For example, with regard to age matching oral contraceptives are used primarily by young, fertile women whereas the risk of cerebral thromboembolic attacks increases exponentially with age. An analysis using the age group 15-44 years as an entity therefore severely underestimates the risk as most affected women will be in their 30s and 40s, when comparatively few healthy women take oral contraceptives. The relevance of age matching is illustrated by the fact that the average odds ratio in previous retrospective studies that used age matching was more than twice the average in the non-age matched studies (table I). This picture did not change appreciably after adjusting for the time at which the studies were conducted.

When these factors are taken into account the Danish results are encouraging as the odds ratios recorded here are in the lower range of those reported previously. These findings suggest that modern oral contraceptives carry a significantly lower risk than the older high oestrogen and middle oestrogen brands (containing 50 μg oestrogen or more). Gerstman *et al*, in a prospective study of the risk of deep venous thromboembolism, reported a 50% increased risk of venous thromboembolism among women taking 50 μg oestrogen preparations compared with women taking 30 μg preparations.[32] These results accord with our findings for cerebral thromboembolic attacks. Thorogood *et al* found an odds ratio for fatal cerebral thromboembolic attack among ever users of oral contraceptives compard with never users of 4·4 (95% confidence interval 0·8 to 24·4) and among present users compared with non-users of 1·4 (NS).[18] At that time minioestrogen pills were the commonest oral contraceptive in use in the United Kingdom. These data are also compatible with the odds ratios recorded in this study. Taken together, available data suggest that oral contraceptives containing more than 50 μg, 50 μg, and 30-40 μg oestrogen are associated with odds ratios for cerebral thromboembolic attacks of about 8-10, 2-4, and 1·5-2·5, respectively, whereas those containing progestogen only seem not to be associated with any increased rise.

Incidences of cerebral thromboembolic attack among women and men aged 15-44

At least six studies have assessed the incidences of cerebral thromboembolic attack among young women and men.[2 4 33-36] Two studied the age group 15-44 as an entity and found no significant sex differences.[33 34] Four studies analysed specifically the incidences among women and men aged under 35, and all found a significantly higher incidence of cerebral thromboembolic attacks and stroke among women than among men. Lidegaard *et al* found an incidence ratio for cerebral thromboembolic attacks between women and men which showed a close covariation with the percentage use of oral contraception (plus the percentage of pregnant women) with increasing age.[36] Thus, if anything, the incidence studies support a causal relation between use of oral contraceptives and cerebral thromboembolic attack.

Trends in incidence of and death rates from cerebral thromboembolic attack among fertile women

Population based diagnosis registers were not available before the early 1960s. Therefore, we have no valid sex specific incidence figures for cerebral thromboembolic attacks from the pre-pill era. Mortality statistics, on the other hand, are available from long before the introduction of oral contraceptives and may therefore provide valid information on sex specific time trend figures. The low case fatality rate among young patients after a cerebral thromboembolic attack (1-2%), however, demands inclusion of a very large population. The case fatality rate for haemorrhagic stroke is several times higher than for thrombotic stroke, cerebral haemorrhage accounting for 80-90% of stroke deaths in young patients. Therefore, any study analysing trends in death rates from cerebral thromboembolic attacks must discriminate between haemorrhagic and thrombotic strokes. Six studies complying with these requirements[37-42] all found an increase in death rate from cerebral thromboembolic attacks among fertile women at the time of the introduction of oral contraceptives, which in all but one study[38] was higher than that among men of the same ages. Although the increase never reached the 5% level of significance (owing to the low absolute numbers of deaths), all six studies found a high percentage increase in the female death rates. Thus there is no evidence in the mortality statistics contradicting a causal relation between oral contraceptives and the risk of cerebral thromboembolic attacks despite several such claims.

In conclusion, no empirical data refute that the proved statistical association between oral contraception and cerebral thromboembolic attacks reflects a causal relation. On the contrary, substantial epidemiological data support a causal influence of oral contraception on the risk of cerebral thromboembolic attacks.

If the established odds ratios reflect a causal relation the proposition of cerebral thromboembolic attacks caused by oral contraception (the aetiological fraction) may be calculated. Before doing this it is important to realise that the use of oral contraception is concentrated among young, fertile women whereas the incidence of cerebral thromboembolic attacks increases exponentially with age.[35] Therefore, it is necessary to apply a percentage of oral contraceptive use matched to the age standardised incidence rates of cerebral thrombo-

embolic attacks—that is, use among the age matched controls (15·2%; table II). For the calculation it is assumed that the relative risks of a cerebral thromboembolic attack among users of middle oestrogen, minioestrogen, and progestogen only oral contraceptives are 3, 2, and 1 respectively. The aetiological fraction (AeF) of oral contraception (OC) in cerebral thromboembolic attack in women of fertile age can then be calculated according to the expression: $AeF = p(RR_{OC} - 1)/p(RR_{OC} - 1) + 1$, where p is the percentage use of oral contraception at a specific age and RR_{OC} the relative risk among users of oral contraceptives. Actually we get: $AeF = 0{\cdot}152 \times 0{\cdot}12(3\text{-}1)/(0{\cdot}152 \times 0{\cdot}12 \times (3\text{-}1) + 1) + 0{\cdot}152 \times 0{\cdot}83(2\text{-}1)/(0{\cdot}152 \times 0{\cdot}83(2\text{-}1) + 1) = 0{\cdot}035 + 0{\cdot}112 = 0{\cdot}147$, where $0{\cdot}152 \times 0{\cdot}12$ is the percentage use of middle oestrogen pills and $0{\cdot}152 \times 0{\cdot}85$ the percentage use of minioestrogen and micro-oestrogen pills. In other words, if the documented association between use of oral contraceptives and cerebral thromboembolic attack is causal and if the odds ratios found in this study are reliable about 15% of cases of cerebral thromboembolic attack among fertile women would not have occurred if none of them had ever taken oral contraceptives.

Among users of oral contraception who suffered a cerebral thromboembolic attack the proportion of attacks caused by the oral contraceptives (aetiological fraction) was two thirds among users of 50 μg preparations, and half among users of 30-40 μg preparations.

PAST USE OF ORAL CONTRACEPTIVES

The reduced risk of cerebral thromboembolic attack among women who had stopped using oral contraception was unexpected as other studies had shown a raised[20] or unchanged risk.[8 9] Possibly women who stop taking oral contraceptives may be particularly health conscious and thus have a reduced risk of cerebral thromboembolic attack because of a healthier lifestyle. Possibly opinion on the risk of oral contraception may differ between Denmark and the United States and Britain, so that in the United States and Britain a sort of "healthy user effect" exists, explaining the increased risk among potentially less healthy former users. Alternatively, opinion may have changed during the past decade, so that in Western countries the factor that generally characterised women who stopped taking oral contraceptives in the 1980s was different from that which characterised women who stopped in the 1970s. For example, women with a familial predisposition may possibly be more effectively dissuaded from taking the pill today than they might have been a decade or more ago. Such a possibility might explain the relatively high number of never users among the cases and consequently the comparatively few former users. In any event, we do not believe that a "hangover" effect of oral contraception protects women against cerebral thromboembolic attack. Further investigations are needed.

SMOKING

The moderately increased risk of cerebral thromboembolic attack among female cigarette smokers accords with several[10 12 16 17 19 43-47] but not all[7 8 13 21 48-53] previous studies of risk among fertile women. Probably the explanation is that where oral contraceptives influence platelet aggregation the influence of cigarette smoking is mediated by a more severe atherosclerosis, which is manifested only several decades later.

There seems to be no synergy between use of oral contraceptives and smoking, only an additive effect. This is also so for women over 35, who are often dissuaded from taking oral contraceptives as they smoke. As the absolute incidence of cerebral thromboembolic attack increases with age, advising these women against oral contraception seems reasonable. The reduced risk among former smokers compared with that of never smokers probably reflects a selection phenomenon, somewhat akin to the putative selection among the former users of oral contraception.

Conclusion

Oral contraceptives are still associated with an increased risk of cerebral thromboembolic attack. The risk decreases with lower oestrogen and progestogen doses and is not demonstrable with minipills (progestogen only pills). The risk is substantially smaller than that recorded with the brands in the 1960s and 1970s. The relative risk of cerebral thromboembolic attacks does not change with increasing age, but the absolute risk, which is multiplied, increases nearly exponentially with age. Hence the absolute risk of cerebral thromboembolic attack increases with age. For a 20 year old woman the absolute attributable risk from using preparations containing 50 μg and 30-40 μg oestrogen is about 6/100 000 and 4/100 000/year, respectively, whereas a woman of 40 increases her risk by about 10 times as much

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Appendix

RECURSIVE GRAPHICAL MODELS

Graphical models were introduced by Darroch *et al*,[54] who showed that the family of models for discrete variables defined in terms of conditional independence between pairs of variables is a subset of the broader class of log linear models for multidimensional contingency tables.

Graphical models are characterised by independence graphs, where vertices represent variables and edges or arrows symbolise conditional relations. A missing edge or arrow between two variables symbolises conditional independence between these two variables. Recursive graphical models[55] partition variables into a linearly ordered set of recursive blocks or levels, representing either design considerations or causal and temporal structures. Variables within the same recursive block are connected by undirected edges whereas directed arrows link variables at different recursive levels.

Figure 2 shows the independence graph resulting from the analysis of the dataset collected in connection with this study of oral contraceptives and cerebral thromboembolic risk. The model includes variables describing some medical diseases and neurological symptoms experienced before the cerebral thromboembolic attack, cigarette smoking, use of different types of oral contraceptives, years of schooling, age, case-control status, and neurological symptoms after the cerebral thromboembolic attack. For brevity we refer to smoking, oral contraceptives, and neurological symptoms before the attack. The recursive structure assumed for the analysis distinguishes between ultimate response variables and risk factors observed before a cerebral thromboembolic attack. Case-control status and age are non-random design variables treated by the analysis as explanatory variables in the sense that the analysis focuses on the conditional distribution of response variables and risk factors given case-control status and age.

The independence graph is both a visualisation of the statistical model and a mathematical object that may be analysed by algorithms from mathematical graph theory. Discrete graphical models are log linear with generators determined by the cliques of the independence graph. Log linear models have collapsibility properties in the sense that some parameters and some statistics can be recovered in marginal distributions of subsets of the complete set of variables. Collapsibility thus breaks large, high dimensional problems down into smaller problems that may be addressed by the standard techniques and methods for analysis by log linear models and will also take care of some of the problems

connected with confounding. For graphical log linear models these properties may be found by analysis of the independence graph with respect to decompositions and separation properties.

The advantage of an analysis by graphical models is, firstly, that the analysis will provide information on the type or order of interaction parameters that we should include in the prospective regression model. With several possible risk factors we should expect some kind of higher order interactions between the effects of different factors, or at least we should consider this possibility. Graphical or log linear modelling, or both, of the conditional distribution of factors given the response variable will take care of this problem in a time effective manner, which may also throw some light on the way the factors are associated in the population (or, at least, among controls).

Figure 2 shows that neurological symptoms are conditionally independent of oral contraceptive use and smoking habits given age and case-control status. It follows that symptoms cannot influence the relation between the lifestyle factors (oral contraception and smoking) and case-control status and that the effect of lifestyle factors may be analysed and estimated in the marginal distribution after collapse over symptoms.

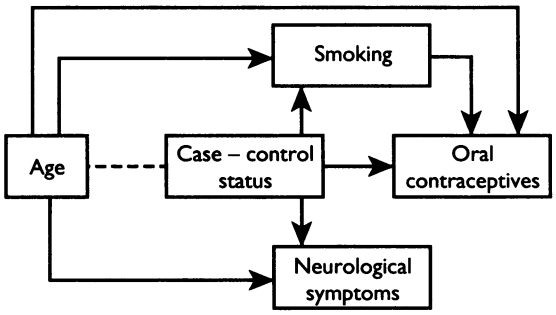

FIG 2—*Independence graph resulting from analysis of dataset collected in Danish study of oral contraceptives and cerebral thromboembolic risk*

To see this, consider a model containing only three variables: cerebral thromboembolic attack (CTA), neurological symptoms (S), and lifestyle habits (oral contraception/smoking) (L). The purpose of the study is to throw some light on the prospective probabilities, P(CTA|S,L), and especially on the interaction parameters quantifying the risk of cerebral thromboembolic attack for different outcomes on lifestyle. To do this we have for practical purposes observed and analysed the retrospective probabilities, P(S,L)|CTA) and found that S and L are conditionally independent given the status of cerebral thromboembolic attack: P(S,L|CTA=P(S|CTA) P(L|CTA). This implies that P(S,L,CTA)=P(S|CTA)P(L|CTA)P(CTA) and therefore that P(CTA|S,L)=P(S|CTA)P(L|CTA)P(CTA)/P(S,L). Expressed in terms of logarithms this means that log $P(CTA|S,L)=\exp(\alpha_{CTA}+\beta_{CTA,L}+\beta_{CTA,S}+\beta_{L,S})$.

The retrospective graphical model postulating conditional independence of risk factors given a cerebral thromboembolic attack thus implies the simplest possible prospective model: a logistic regression model with no interaction between the effect of symptoms and lifestyle habits on the risk of cerebral thromboembolic attack. The relation between the interaction parameters of the prospective model and the retrospective probabilities—for example, $\beta_{CTA,L}=\log P(L|CTA)$ also means that risk parameters may be estimated in the marginal distributions of lifestyle and neurological symptoms separately given cerebral thromboembolic attack.

Note that age is disregarded in the above discussion. The arguments generalise, however, without problems to a discussion of the conditional distribution of cerebral thromboembolic attack, symptoms, and lifestyle factors given age.

Note also that conditional association between two factors does not have to imply that there must be some kind of interaction between the effect of these factors in the prospective model. In the example considered here symptoms and lifestyle factors are multidimensional with conditionally related components. To determine whether or not there is interaction between the effects of the separate components we must perform a more careful parametric log linear analysis of the conditional relations between these factors given cerebral thromboembolic attack. These analyses may, however—owing to the collapsibility properties—be performed separately for the two sets of possible risk factors without any risk of confounding between the sets. In this paper we have concentrated on the results pertaining to the use of oral contraception and smoking of primary concern for the study.

One additional advantage of the graphical models is that techniques for analysis of ordinal categorical data[56] and analysis by exact conditional methods[57]—for example, multidimensional generalisation Fisher's exact test for 2×2 tables—may easily be integrated in the analyses together with the usual techniques for log linear modelling. In this study we have used a partial rank correlation coefficient based on Goodman and Kruskall's γ coefficient for r×c tables.

The γ coefficient for an r×c table is a rank correlation comparable to Kendall's τ. The partial γ coefficient for κ r×c tables is calculated as a weighted mean of the κ separate γ coefficients. For κ 2×2 tables it may be argued that the partial γ coefficient and the Mantel-Haenszel statistic attempt to measure the same kind of interaction. Firstly, there is a simple one to one relation between the odds ratio statistic and the γ coefficient for 2×2 tables: odds ratio=$(1+\gamma)/1-\gamma)$. Secondly, the Mantel-Haenszel statistic is given as a weighted mean of the κ odds ratio statistics. The weights are, however, not directly comparable to the corresponding weights used for the partial γ coefficient. There is therefore no simple relation between the two measures, even though they attempt to measure the same interaction.

We emphasise that there is no principal conflict between the analysis by graphical models and the more conventional techniques for analysing retrospective data from case-control studies by multiple logistic regression analysis. Both approaches accept a logistic regression model as the appropriate model for the prospective probabilities.

Correction for trend in oral contraceptive types during study period

As the controls stated their specific use of oral contraceptives (OC) in 1990, and the cases sometimes between 1985 and 1990, the calculation of odds ratios for different types of pills (according to their oestrogen content) had to account for the time trend in the distribution between pills with different hormonal content during the study period. As the changes in distribution during 1985-9 were roughly linear adjustment was based on the development from 1987 to 1990. The corrected (OR_{corr}) were calculated as a product of the crude odds ratio and a cross product ratio (OR_{year}) according to the relation $OR_{corr}=OR_{crude}\times OR_{year}$, where $OR_{year}=(p(OC_{90})\times p(1-OC_{87}))/(p(OC_{87})\times p(1-OC_{90}))$. [p=Percentage use of oral contraception at a specific age.] These corrections were made for each pill type with the assumption (*a*) that smoking habits, education, and medical diseases were constant during 1985-90, so that none of these factors changed their influence on the risk of cerebral thromboembolic attack implied for a specific pill type during these years, and (*b*) that no other confounding influence changed during 1985-90. In the estimations of $p(OC_{87})$ the assumption was made that the changes from 1987 to 1990 in the total use of a specific type of oral contraception were the same within each five year age group during this period and that the relation between former and never users of oral contraception was constant from 1987 until 1990. These assumptions were operationalised by calculating with constant cross products between age groups and oral contraception status in 1990 and 1987. The corrected odds ratios were finally adjusted for the influence of the included confounders.

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Effect of stress management on blood pressure in mild primary hypertension

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Abstract

***Objective*—To establish whether stress management had a larger effect than a control treatment on resting blood pressure, ambulatory blood pressure, and left ventricular mass.**

***Design*—A 12 week baseline period of habituation to measurement of blood pressure was followed by randomisation to either stress management or mild exercise for six months and follow up six months later.**

***Setting*—General practice, district general hospital, and medical school.**

***Patients*—Of the 184 patients aged under 60 with mild primary hypertension who entered the baseline habituation period, 88 were excluded because they failed to meet the entry criteria or they withdrew from the study. The remaining 46 men and 50 women underwent treatment.**

***Interventions*—10 clinical sessions and daily practice at home of either stress management based on relaxation or non-aerobic stretching exercises. Mildly stressful 15 minute interviews before and after treatment.**

***Main outcome measures*—Diastolic and systolic blood pressure in the clinic and during 12 hours of ambulatory recording, and left ventricular mass measured by echocardiography.**

***Results*—The patients' blood pressure fell during habituation (systolic pressure from 152 mm Hg to 140 mm Hg, diastolic pressure from 98 to 93 mm Hg), but neither resting nor ambulatory blood pressure was changed by the treatments. Left ventricular mass was also unchanged. Blood pressure rose during the stressful interview, but this rise was reduced by stress management (systolic pressure rose by 7·4 mm Hg before treatment and by 3·7 mm Hg after treatment).**

***Conclusion*—Stress management of a type advocated for treating mild primary hypertension is ineffective in lowering blood pressure in patients who are well habituated to measuring blood pressure.**

Introduction

Raised blood pressure is associated with increased risk of cardiovascular disease. Even the mild increases in blood pressure found in up to a fifth of adults are associated with a higher incidence of myocardial