

Contraceptives and cerebral thrombosis: a five-year national case-control study[☆]

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Abstract

The object of this study was to assess the influence of oral contraceptives (OCs) on the risk of cerebral thromboembolic attacks (CTA) including thrombotic stroke and transitory cerebral ischemic attacks. A 5-year case-control study including all Danish hospitals was conducted. All women 15–44 years old suffering a first ever CTA during the period January 1, 1994 to December 31, 1998, were included. Controls were selected annually, 600 per year in 1994–1995, 1200 per year 1996–1998. Response rates for cases and controls were 88% and 90%, respectively. After exclusion of nonvalid diagnoses, pregnant women, and women with previous thrombotic diseases, 626 cases and 4054 controls were available for analysis.

A multivariate matched analysis was performed. Controls were matched to cases within 1-year age bands. Adjustments were made for the following potential confounders: year, length of OC use, smoking, hypertension, migraine, family CTA, and years of schooling. There were 212 and 1208 current users of OCs among cases and controls, respectively.

The risk of CTA among current users of OCs decreased significantly with decreasing estrogen dose (nonusers reference): OCs with 50 μg , 30–40 μg , 20 μg ethinyl estradiol (EE) and progestin-only pills implied adjusted odds ratios (ORs) (95% CI) of 4.5 (2.6–7.7), 1.6 (1.3–2.0), 1.7 (1.0–3.1), and 1.0 (0.3–3.0), respectively. Current users of OCs with second- (levonorgestrel or norgestimate) and third- (desogestrel or gestodene) generation progestins combined with 20–30 μg EE had ORs of CTA of 2.2 (1.6–3.0) and 1.4 (1.0–1.9), respectively. After correction for differences in estrogen dose, the third- to second-generation risk ratio was 0.6 (0.4–0.9; $p = 0.01$).

In conclusion, high dose OCs and OCs with second-generation progestins were associated with the risk of CTA. The risk increased 2.5 times with estrogen dose increasing from 20 to 50 μg EE, and users of low-dose OCs with second-generation progestins had a 61% higher risk-association of CTA than users of OCs with third-generation progestins. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Oral contraceptives; Cerebral thrombosis; Thrombotic stroke; Transitory cerebral ischemic attack; Thrombosis

1. Introduction

It is generally accepted that the increased risk of ischemic stroke among current users of oral contraceptives (OCs) has been reduced with the introduction of low-dose OCs with less than 50 μg ethinyl estradiol (EE). The influence of the different types of progestins, however, is still controversial. Of four studies, specifically exploring the influence of low-dose OCs with different types of progestins on the risk of ischemic stroke [1–4], three found a significantly increased risk among current users of OCs with second-generation progestins (levonorgestrel or norgesti-

mate) [1,3,4], and two found a significantly increased risk among users of OCs with third-generation progestins [1,3] (Table 1).

Incidence data from Denmark over the period 1980–1993 have demonstrated an exponential increase in the incidence rate of ischemic stroke and transitory cerebral ischemic attacks [collectively, cerebral thromboembolic attacks (CTA)] with increasing age and a significantly decreasing incidence rate over time among young women [5]. During the same period, the use of low-dose OCs with 30–40 μg EE became dominant, and the majority of users in Denmark changed from OCs with second- to OCs with third-generation progestins [4]. Unlike some other countries in Europe, the majority of Danish current users of OCs are still taking pills with third-generation progestins, and the distribution of different types of OCs according progestin type has been fairly stable during the study period 1994 through 1998 (Fig. 1).

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Table 1
Recent studies on low-dose OCs and ischaemic stroke

Study [reference]	Nationality	PDS*	Cases/ controls	OR 2nd/3rd	95% CI 2nd/3rd
WHO [1]	Multicenter	89–93	489/3967	2.7/1.7	1.8–4.1/1.2–2.5
Schwartz [2]	USA	91–95	175/1191	1.1 [‡]	0.5–2.2
Heinemann [3]	Europe	93–96	220/439 [†]	2.7/3.4	1.5–4.6/1.9–6.4
Lidegaard [4]	DK	94–95	233/1074	2.4/1.3	1.4–4.2/0.8–2.2
Lidegaard [this study]	DK	94–98	626/4054	2.2/1.4	1.6–3.0/1.0–1.9

* PDS = period of data sampling; OR = odds ratio; 2nd = OCs with second-generation progestins (levonorgestrel or norgestimate); 3rd = OCs with third-generation progestins (desogestrel or gestodene).

[†] Figures based on community controls.

[‡] Low-dose OCs with first- and second-generation progestins combined.

Since 1977, all hospitalized patients in Denmark have been registered in the Danish National Patient Register (NPR) with diagnosis codes according to World Health Organization's (WHO) International Classification of Diseases (ICD). Since 1994, the 10th edition of ICD has been in use in Denmark. Cerebral thromboembolism includes, according to ICD-X, the sub-diagnoses cerebral infarction I 63.0–I 63.3 and I 63.5–63.9, cerebral embolism I 63.4, transitory cerebral ischemic attacks (TIA) G 45, as well as the unspecified cerebral apoplexy I 64.9, of which thrombotic strokes have been found to constitute 80–90%.

A 5-year prospective case-control study on OCs and cerebral thrombosis was initiated in 1994. The aim of the

study was to assess the influence of estrogen dose and progestin types of OCs on the risk among young women of developing CTA. The results from the first 2 study years have been published elsewhere [4]. This report presents the final results of the 5-year study period.

2. Material and methods

2.1. Cases

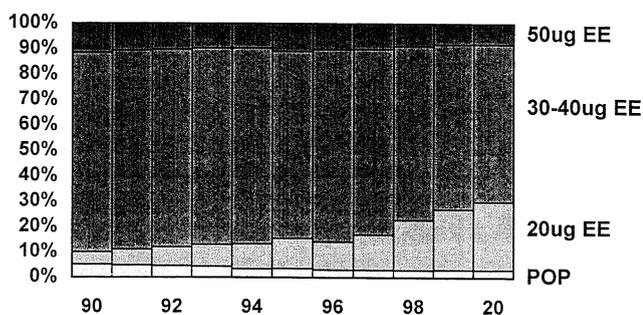
All women 15–44 years old who suffered a CTA during the study period were included in the study. Women with CTA or other thrombotic diseases before 1994 [1980–1993] were identified in the register and primarily excluded from the study in order to include only first-ever events. Women who were registered more than once during the 5-year period were recorded according to their first discharge diagnosis.

The submitted questionnaires included information about use of OCs, including specific current use at the time of admittance to hospital, length of that use, time since last use of OCs among former users, smoking habits (never smokers, former smokers, 1–10 cigarettes/day, 11–20 cigarettes/day, > 20 cigarettes/day), treated hypertension, pregnancy, previous thrombotic stroke, previous venous thromboembolism (VTE), previous myocardial infarction, migraine, coagulation disturbances, hyperlipidemia, diabetes, heart diseases, family history of specific thrombotic diseases, persisting clinical symptoms from the CTA, length of schooling (as a proxy for social class), diagnostic examinations conducted [computer tomography (CT scan) or magnetic resonance imaging (MRI scan)], and each woman's own opinion on any other possible contributing factor (open question).

2.2. Controls

For each of the years 1994 and 1995, a control group of 600 women was established, age-matched to CTA patients. During the period 1996–1998, 1200 women 15–44 years

Sale of oral contraceptives (OCs) in Denmark 1990–2000.
Estrogen dose (ethinylestradiol (EE))



Progestin types in 20–40ug OCs

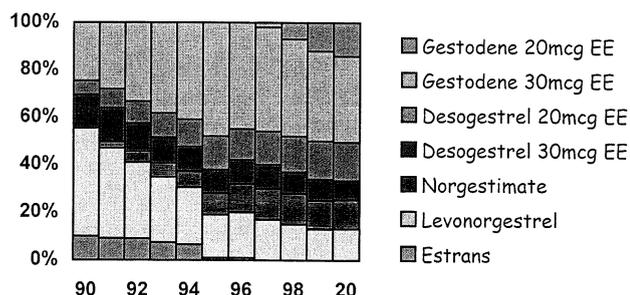


Fig. 1. Sale of OCs in Denmark 1990–2000.

old, were randomly selected from the Central Person Register (CPR), which includes all Danish people older than 5 days. By this design it was assured that the control group corresponded to the cases in terms of both age and time (year) to comply with changes in use of different types of OCs during the study period (change from higher to lower dose OCs; Fig. 1). The control women were selected at random from the CPR. Age differences between cases and controls because of secondary exclusions were adjusted for in the analysis.

The control questionnaires included the same information as the case questionnaires. Of 4732 control women contacted, 4245, or 89.7%, returned a completed questionnaire.

2.3. Identification of cases

The identification of cases was done during the year after the admittance to hospital, or on average about 1 year after the attack. The addresses of the identified women were provided from the CPR. Permission to conduct the study was received from the National Health Board (6516–48-1994), the Board of Registers (1994–1200-460), and the Ethical Scientific Committees (KA 94124 m). The heads of the involved departments were asked for permission to send a questionnaire to each of the affected women.

To ensure a high validity of the included cases, only women with a discharge diagnosis of CTA, with confirmation from the department that was responsible for the discharge diagnosis, and who themselves confirmed the diagnosis, were included in the study.

2.4. Categorization of users of OCs

Current users of OCs were categorized according to four axes:

- I. Four groups according to estrogen dose: 50 µg EE; 30–40 µg EE, including the sequential brands; pills with 20 µg EE; and progestin-only pills.
- II. Five groups according to progestin type: (a) estranes including norethisterone, lynestrenol, and ethynodiol; gonanes including (b) norgestrel and levonorgestrel, (c) norgestimate, (d) desogestrel, and (e) gestodene.
- III. Three groups according to duration of use: <1 year, 1–5 years, >5 years.
- IV. Three groups according to a combined categorization in first-generation OCs, including all OCs with 50 µg EE. OCs with 30–40 µg EE and levonorgestrel, norgestrel, or norgestimate constituted the second-generation group, and OCs with 20–40 µg EE and desogestrel or gestodene were categorized as third-generation OCs. Norgestimate was categorized as a second-generation product because it is partly metabolized to levonorgestrel.

Current use was defined as use of OCs at the time of admission (cases) and time of receiving the questionnaire (controls). Former use was defined as any previous use among women not currently taking OCs.

2.5. Statistical analysis

The data were analyzed by graphical log linear models for multidimensional contingency tables [6,7] to identify potential confounders, and thereafter by conditional logistic regression. Test of significance was performed by using both chi-square test and, in case of ordinal variables, the partial Goodman-Kruskal gamma. Level of significance was set at 5%. Potential confounders were defined as variables with a significant association to the outcome as well as to the exposure. The final set of confounders to adjust for was determined by graphical modeling [8]. Controls were matched to cases within 1-year age bands. Calendar year was included as a potential confounder in the analysis. In case of no confounding influence, a supplementary analysis with year as match variable within 1 year was performed.

Three sets of risk estimates were calculated as odds ratios (ORs) with 95% confidence limits. The first set (crude ORs) was the risk estimates after matching for age and calendar year. The second set (adjusted ORs) was risk estimates adjusted for all the included confounders. The third set (corrected ORs) was estimates adjusted for the other OC-axes. Thus, the influence from, e.g., a certain progestin type versus another was adjusted for differences in duration of OC use as well as differences in estrogen dose to determine the isolated influence of the progestin type. In practice, the reference group in these analyses had a certain distribution according to length of use and to estrogen doses. The other progestins were standardized according to the length of use and to the estrogen dose, so that any difference in the corrected estimates were due to differences in influence from progestin types.

In previous studies, differences in risk between never-users and former users of OCs were demonstrated. Because the proportion of never-users of OCs is increasingly small, and because these never-users of OCs could have special characteristics compared with ever-users, nonusers (never-users + former users) were considered to be the reference group. The assessment of the risk among former users of OCs was done with never-users of OCs as reference.

3. Results

During the study period, 1037 women were identified alive at discharge from hospital in the NPR (Table 2). Forty-nine women had died since discharge, in 18 women the diagnosis was uncertain (information from departments); for 29 women no permission to contact was given by the departments, primarily because of mental retardation; for 22 cases no response was received from the department; and 34 women had no available address or were not present

Table 2
Inclusion and exclusions of cases and controls

	Cases		Controls	
	Excluded	Remaining	Excluded	Remaining
Identified in	NPR*	1,043	CPR	4,800
Non-Danish inhabitants	6	1,037	0	4,732
Died since discharge	49	988	0	
Wrong diagnosis (information from dept)	11	977	0	
Diagnosis not confirmed (information from dept)	7	970	0	
No permission to contact	29	941	0	
Lack of permission to contact	22	919	0	
No available address/not at address	34	885	68	4,732
Submitted questionnaires (100%)		885		4,732
Returned questionnaires (response rate)	(88.1%)	780	(89.7%)	4,245
Previous stroke (information from case)	24	756	6	4,239
Invalid diagnosis (information from case)	77	679	0	4,239
Refuse invitation to participate	15	664	20	4,219
Valid for analysis		664		4,219
Pregnant	12	652	146	4,073
Previous VTE	18	634	19	4,054
Previous AMI	5	629	0	4,054
Severe general disease	3	626	0	4,054
Included in analysis		626		4,054

* NPR = National Patient Register; CPR = Central Person Register.

at the address. Thus, 885 questionnaires were submitted. One reminder was sent out to nonresponders within 3 months after the primary application.

We received 780 (88.1%) questionnaires. All except 15 women agreed to participate. Of the remaining 765 cases, 24 indicated previous stroke, 18 previous venous thromboembolism, 5 previous myocardial infarction (one of these also previous venous thromboembolism), 12 that they were pregnant at the time of the attack, 77 that they had an uncertain diagnosis (primarily patients with TIA), and 3 that they had a severe general disease. Thus, 626 women were available for analysis.

Of the 626 included cases, 401 (64%) had cerebral infarction and 225 (36%) TIA. The distribution of OC use and potential confounders in these two groups of cases did not differ significantly. Consequently, all the cases were analyzed together. Of the included women with cerebral infarction, 93% had undergone a CT scan and 56% an MRI scan, 98% at least one of these. Of the cases with TIA, 82% had undergone CT scan and 39% an MRI scan, 88% at least one of these examinations.

Of the 4245 controls returning a questionnaire, 146 were pregnant, 19 had previously had VTE, 6 had previous CTA, and 20 women did not want to participate, leaving 4054 available for analysis.

3.1. OCs and CTA

Among the 626 women with CTA, 212 (33.9%) were current users of OCs, 301 (48.1%) were former users, 4 of them were currently on cyproterone (Diane Mite), 96 (15.3%) were never-users of OCs, and 17 (2.7%) were

non-specified non-users. Among the controls, 1208 (29.8%) were current users of OCs, 2025 (50.0%) were former users, 38 (1%) were on cyproterone, 713 (17.6%) were never-users, and 71 (1.7%) non-specified non-users. The detailed distribution of current users of different types of OCs among cases and controls is given in Table 3. Of the 212 CTA users of OCs, 198 (93%) could specify the brand taken. Among 1208 control users, 1186 (98%) could specify the brand. The 14 cases and 22 controls who did not specify the brand were not included in the multivariate analysis on differences between sub-types of OCs.

The crude estimates (Table 4) demonstrate a decreasing risk by length of OC use, a higher risk for second- than for third-generation OCs, and a decreasing risk with decreasing estrogen dose. After adjustment for smoking, migraine, and years of schooling, no major changes in the crude trends were observed. Year, hypertension, diabetes, family CTA, family acute myocardial infarction (AMI), family VTE, coagulation disturbances, hyperlipidemia, and heart disease were all tested, but were without confounding influence or without confounding influence after adjustment for the included confounders. Adjusted risk estimates for specific combinations of estrogen dose and progestin types are indicated in Table 5.

The difference observed between second- and third-generation OCs could be influenced by differences in length of use between the two groups, to differences in associated estrogen dose, or to a different impact of the two progestins. To discriminate among these influences, the third-generation pills were corrected according to length of use and to estrogen dose, so that the distribution was the same as for the reference group of second-generation users. These cor-

Table 3
Use of different types of OCs among cases and controls

N (%) [*]	Estrans	Levonorgestrel	Norgestimate	Desogestrel	Gestodene	Total
Cases						
50 µg EE [†]	12 (6.1)	14 (7.1)	—	—	—	26 (13.1)
30–40 µg EE	11 (5.6)	48 (24.2)	22 (11.1)	12 (6.1)	57 (28.8)	150 (75.8)
20 µg EE	—	—	—	16 (8.1)	2 (1.0)	18 (9.1)
POP [*]	4 (2.0)	0 (0.0)	—	—	—	4 (2.0)
Specified						198 (100)
Unspecified						14 (-)
Total						212
Controls						
50 µg EE	30 (2.5)	16 (1.3)	—	—	—	46 (3.9)
30–40 µg EE	77 (6.5)	182 (15.3)	118 (9.9)	90 (7.6)	486 (41.0)	953 (80.4)
20 µg EE	—	—	—	129 (10.9)	30 (2.5)	159 (13.4)
POP	25 (2.1)	3 (0.2)	—	—	—	28 (2.4)
Specified						1186 (100)
Unspecified						22
Total						1208

* Percent of specified users

† EE = ethinyl estradiol; POP = progestin-only pills.

rected estimates, thus, demonstrate the difference between the progestin types with the same pattern of use according to length of use and to estrogen dose. We still found a significant difference: OCs with third-generation progestins implying 38% less risk ($p = 0.011$). In the analysis with match also for calendar year, the risk estimate was 34% lower for OCs with third- compared with second-generation progestins ($p = 0.034$).

With the 30–40 µg EE pills as reference, and after correction for differences in duration of use and progestin types, we still found a significant trend according to estrogen dose (Table 4). An analysis of the specific progestin types demonstrated significantly elevated ORs for levonorgestrel and norgestimate as compared with desogestrel and gestodene. On the other hand, no trend in risk according to length of use was apparent after control for progestin types and estrogen dose.

The conclusion, therefore, is that the risk of CTA among current users of OCs is not influenced by length of use, is clearly influenced by estrogen dose, and is significantly influenced by the progestin types. According to this study, OCs with 50 µg EE increases the risk of CTA about 4.5 times; middle-dose OCs with 30 µg EE combined with second-generation progestins increased the risk 2.2 times; whereas risk estimates of middle- and low-dose (20–30 µg EE) OCs with the third-generation progestins (desogestrel or gestodene) suggested a somewhat smaller increase in risk of CTA, about a 40% increase. Progestin-only pills did not confer women any risk of CTA.

3.2. Other risk factors

We still have about 40% smokers in women of reproductive age in Denmark. Cigarette smoking increased the

risk of CTA 1.5–1.8 times compared with women who had never smoked cigarettes (Table 6). Former smokers had a decreased risk of CTA, OR 0.72 (0.5–1.0). There was no significant association between the risk of CTA and the number of cigarettes smoked after adjustment for years of schooling.

Hypertension has a low prevalence in young women, 1.4%. Hypertension increased the risk of CTA five times (Table 6). Migraine more than once a month occurred in 6.4% of the controls and in 17% of cases. Migraine increased the risk of CTA 3.2 times. Diabetes was present in 0.4% of the controls and 4.3% of cases. It increased the risk of CTA 5.6 times.

Thrombotic diseases in the family increased the risk of CTA significantly. Myocardial infarction, CTA, and VTE in one or both parents increased the risk of CTA 44%, 36%, and 47%, respectively (Table 6).

Women with hyperlipidemia and coagulation disturbances had an 11–12-fold increased risk of CTA, and women with heart disease a 12.7 times increased risk of CTA.

The risk decreased by length of schooling, which was used as a proxy for social class (Table 6). Compared with women with 7–9 years of schooling, women with 11–12 years had a 56% (0.34–0.56) decreased risk of CTA.

3.3. Interaction and effect modification

There was no interaction or effect modification between any of the other risk factors and OC use. This finding principally indicates that the total risk among women with combined risk factors corresponds to a multiplication of the ORs of the separate risk factors.

Table 4
Risk of CTA in users of different types of OCs

	Cases/controls n/n	Crude* OR 95% CI	Adjusted† OR 95% CI	Corrected‡ OR (95% CI)
Never use	96/713	1 (reference)	1 (reference)	
Former use	301/2,025	0.7 0.6–0.9	0.7 0.6–1.0	
Nonuse	397/2,738	1 (reference)	1 (reference)	
Current use	212/1,208			
Duration of use (years)				
<1	23/173	2.7 1.7–4.3	2.7 1.7–4.4	1 (reference)
1–5	54/412	2.0 1.4–2.9	2.0 1.4–2.9	1.0 0.6–2.0
>5	121/596	1.9 1.5–2.4	1.8 1.4–2.3	0.9 0.5–1.7
Generation				
First	26/46	4.7 2.8–7.9	4.5 2.6–7.7	1.8 1.0–3.3
Second	70/300	2.2 1.6–3.0	2.2 1.6–3.0	1 reference
Third	87/735	1.3 1.0–1.8	1.4 1.0–1.9	0.6 0.4–0.9
Estrogen dose				
50 µg EE	26/46	4.7 2.8–7.9	4.5 2.6–7.7	2.8 1.5–5.2
30–40 µg EE	150/953	1.7 1.3–2.1	1.6 1.3–2.0	1 reference
20 µg EE	18/159	1.6 0.9–2.8	1.7 1.0–3.1	1.1 0.5–2.2
POP	4/28	1.0 0.3–2.9	1.0 0.3–3.0	Not estimated
Progestin type				
Estrans	23/107	2.1 1.3–3.5	1.6 1.0–2.7	0.5 0.3–1.1
Levonorgestrel	62/198	2.6 1.9–3.6	2.6 1.8–3.6	1 reference
Norgestimate	22/118	2.4 1.5–4.1	2.6 1.6–4.4	1.1 0.6–2.1
Desogestrel	28/219	1.4 0.9–2.2	1.6 1.0–2.5	0.7 0.4–1.4
Gestodene	59/516	1.3 1.0–1.8	1.3 1.0–1.9	0.6 0.4–1.0

* Crude OR: Matched by 1 year age groups and year.

† Adjusted for age, year, smoking, migraine, years of schooling. Tested variables without confounding influence, or with no confounding influence, after adjustment for the included confounders: hypertension, diabetes, hyperlipidemia, coagulation disturbances, heart disease, family CTA, family AMI, and family VTE.

‡ Generation: Corrected for differences in estrogen dose and length of use. Estrogen dose: Corrected for duration of use and progestin types. Progestin type: Corrected for duration of use and estrogen dose.

4. Discussion

4.1. Validity of diagnoses

Four attempts were made to ensure the validity of the diagnoses. Firstly, all the cases were identified in the NPR, which is based on doctors' discharge diagnoses from the involved departments. Secondly, the head of each department in which an afflicted woman had been treated was asked for permission to send a questionnaire to the woman. In those instances where the department was aware of a wrong diagnosis on the discharge letter or a later revised

diagnosis, the case was excluded. Thirdly, each woman included in the analysis confirmed her own diagnosis. And fourthly, a very high percentage of cases had their diagnosis confirmed by a CT and/or an MRI scan.

For these reasons, the diagnoses included in the final analysis seem to have very high percent to represent true CTA.

4.2. Validity of exposures

Women generally have a fair recall of their contraceptive habits [9–12]. The cases were asked about use of OCs at the

Table 5
Adjusted risk estimates for specific combinations of estrogen dose and progestin types; non-users of OCs reference

OR 95% CI	Estrans	Levonorgestrel	Norgestimate	Desogestrel	Gestodene	Cyproterone
50 µg EE*	2.7 1.3–5.8	8.2 3.7–18.1	—	—	—	—
30–40 µg EE	1.1 0.5–2.2	2.1 1.4–3.0	2.6 1.6–4.4	1.4 0.7–2.7	1.3 1.0–1.9	1.4 0.5–4.3
20 µg EE	—	—	—	1.7 0.9–3.1	1.6 0.3–7.6	—
POP†	1.0 0.3–3.0	—	—	—	—	—

* EE = ethinyl estradiol; POP = progestin only pills.

Table 6
Influence of other risk factors on the risk of cerebral thromboembolism

Risk factor	Cases	Controls	Crude OR*	Adjust OR [†]	95% CI
Smoking ¹	n (%)	n (%)			
Never smokers	184 (29.4)	1,699 (42.0)	1	1	Reference
Former smokers	74 (11.8)	786 (19.4)	0.7	0.7	0.5–1.0
1–10 per day	108 (17.3)	576 (14.2)	1.6	1.5	1.1–1.9
11–20 per day	191 (30.6)	755 (18.7)	1.9	1.8	1.4–2.4
>20 per day	68 (10.9)	230 (5.7)	1.9	1.6	1.2–2.3
Hypertension ²	66 (10.5)	58 (1.4)	6.3	5.0	3.3–7.4
Migraine ³	107 (17.1)	258 (6.4)	3.2	3.2	2.5–4.2
Diabetes ⁴	27 (4.3)	15 (0.4)	12.3	5.6	2.5–12.3
Family AMI ⁵	145 (23.2)	520 (12.8)	1.6	1.4	1.2–1.8
Family CTA ⁶	66 (10.5)	239 (5.9)	1.4	1.4	1.0–1.8
Family VTE ⁷	53 (8.5)	193 (4.8)	1.6	1.5	1.1–2.1
School (years) ⁸					
7–9	189 (30.3)	590 (14.6)	1	1	Reference
10	214 (34.3)	1,339 (33.1)	0.5	0.5	0.4–0.7
11–12	221 (35.4)	2,118 (52.3)	0.4	0.4	0.3–0.6
Hyperlipidemia ⁹	57 (9.1)	24 (0.6)	14.9	11.0	6.5–18.9
Coag. disturb. ¹⁰	34 (5.4)	12 (0.3)	19.4	12.5	5.7–27.2
Heart diseases ¹¹	29 (4.6)	13 (0.3)	15.0	12.7	6.2–25.8

* Crude: Matched for age and year.

† Adjusted for other risk factors.

¹ Adjusted for OC use, migraine, coagulation disturbances, years of schooling.

² Adjusted for diabetes and family AMI.

³ Adjusted for OC use.

⁴ Adjusted for hypertension and hyperlipidemia.

⁵ Adjusted for hypertension, family CTA, and VTE.

⁶ Adjusted for family AMI and family VTE.

⁷ Adjusted for family AMI and family CTA.

⁸ Adjusted for OC use, smoking, hyperlipidemia.

⁹ Adjusted for diabetes, coagulation disturbances, years of schooling.

¹⁰ Adjusted for smoking, hyperlipidemia, coagulation disturbances.

¹¹ Adjusted for coagulation disturbances.

time of their admission to hospital about 1 year after the event. Both cases and controls were given a list of available brands of OCs with the questionnaire. Ninety-three percent of the cases could specify the brand taken. Among the controls, the actual use/nonuse of OCs was stated, and thus recall bias was not an issue, illustrated by only 2% of the control woman did not specify the brand taken.

4.3. Nonresponse

Nonresponders are always of concern in case-control studies. The available information about the nonresponders shows that their age distribution was similar to that of the responders. A response rate among both cases and controls of about 90% implies that response-selection probably had little influence in this study. The mortality in young women with thrombotic stroke is about 2%. This circumstance indicates that achieving information only from survivors could not have biased our results substantially.

4.4. Preferential prescribing

In many countries including Denmark, the new pills with third-generation progestins have been perceived as safer

than the older pills, specifically concerning thrombotic events. Therefore, many gynecologists and general practitioners have prescribed these new pills to women who have an anticipated increased thrombotic risk [13]. This type of selection in prescribing OCs implies a potential bias in nonrandomized epidemiologic studies, the so-called “prescribing bias” or “preferential prescribing.”

Family disposition of thrombotic stroke and myocardial infarction, hypertension, diabetes, and smoking are probably the most important confounders to adjust for to account for any prescribing bias. All these variables were included in the multivariate analysis, and adjustment for these confounders did not confer dramatic changes in the risk estimates.

It is important for people outside of Denmark to be aware that we did *not* have a “pill crisis” in Denmark after the “Dear Doctor” letter¹ in UK in late 1995, which is illustrated in Fig. 1, and there has been no media storm as we saw in other countries. Among our OC users, we still have about two-thirds who take OCs with third-generation progestins.

4.5. Referral and diagnostic bias

Referral selection and diagnostic selection are the circumstances that users of OCs may be more likely to be

referred or investigated in case of symptoms of CTA than nonusers of OCs. If any such selection is in effect, the risk of OCs is overestimated. As practically all young women with stroke in Denmark are transferred to hospital, that bias is not likely to be in effect for cerebral infarction. For TIA, on the other hand, this bias is a possibility. Because the risk of TIA, however, did not differ from the risk of cerebral infarction, referral bias probably did not have a major influence on that diagnosis.

4.6. Evaluation of results

The results from this study as concerns the overall risk and risk according to estrogen doses are in accordance with the results from five recent studies [1–4,16]. There is good agreement in different studies on the risk of thrombotic stroke in users of OCs with second-generation progestins, with risk estimates of 2.7 in the WHO study [1], 2.7 in the Transnational Study [3], 2.4 in our first 2 study years, and 2.2 in our final analysis. In the pooled results from two US studies [2], the majority of cases and controls had used low-dose OCs with norethindrone (first-generation progestin), and they found no elevated risk in their American group.

On the other hand, there is no impressive agreement on the influence of OCs with third-generation progestins. WHO found an estimate of 1.7, the Transnational study group an OR of 3.4, and we an OR of 1.4 in the final analysis (Table 1). Our progestin-specific results, thus, are in good agreement with the WHO data, and our slightly smaller estimates could be explained by differences in screening for hypertension in Danish women compared with women in the different centers participating in the WHO study. In the Transnational Study, the risk estimate for OCs with third-generation progestins decreased from 6.4 to 2.4 (former-users reference) if the women's blood pressure was checked [3]. A different distribution of never-users and former users in the reference group in different countries could also have brought smaller differences between different studies. The number of third-generation users in cases controls in the WHO study were 8/15, in the Transnational study 45/92, and in our study 87/735. A weighted estimate according to these three studies produces an average OR of 1.6.

The risk of CTA in users of OCs with 20 µg EE and with 30–40 µg EE was identical, although only significantly increased for the latter group.

In the general evaluation of thrombotic risks in users of OCs, it is important not only to consider the relative risk, but also the absolute risk, the case-fatality rate for each diagnosis as well as the consequences for the survivors with stroke.

The incidence rate of CTA in young women is low: 2/100,000 per year for thrombotic strokes and 1/100,000 for TIA in the age group 15–24 years [15]. An increase in this risk by 50% or even 100% still implies very little absolute

risk. For women above 40 years, on the other hand, the absolute risk of CTA is about 20/100,000 per year. Therefore, these women should not have additional risk factors if they are to use OCs, and for them, together with young women with risk factors of stroke, OCs with third-generation progestins could be a natural first choice.

4.7. Other risk factors

The increased risk of CTA among women smoking cigarettes has been found in many previous studies, including our case-control study from 1993 [16]. Also in that study we were able to demonstrate a dose-response relationship. In this study the increasing risk with the number of cigarettes smoked disappeared with control for years of schooling, a proxy for social class.

The risk estimates of hypertension, migraine, and diabetes are in agreement with other studies [1,14,16]. The adjusted estimate for diabetes was only about one half of the crude risk estimate, suggesting that hypertension may contribute significantly to the risk of CTA in diabetic women.

We had expected that family history of CTA increased the risk of CTA more than family AMI or family VTE. No significant difference was observed, however, between these dispositions, all increasing the risk of CTA 36–47%. This circumstance still makes it meaningful to ask women about thrombotic dispositions before prescribing OCs.

The risk estimates of hyperlipidemia, coagulation disturbances, and heart diseases are overestimated due to the circumstance that many of the cases were not aware of these conditions before their stroke. The cerebral event was responsible for these women being investigated, thereby assessing these conditions. No such event was present among the controls that, therefore, are generally not aware of these conditions. Unfortunately, it is not possible to adjust for this “bias by indication.”

Note

1. The “Dear Doctor” letter was a warning against OCs with third generation progestins.

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References

- [1] WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect on stroke of different progestagens in low-dose oestrogen oral contraceptives. *Lancet* 1999;354:301–2.

- [2] Schwartz SM, Petitti DB, Siscovick DS, et al. Stroke and use of low-dose oral contraceptives in young women. *Stroke* 1998;29:2277–84.
- [3] Heinemann LAJ, Lewis MA, Spitzer WO, Thorogood M, Guggenmoss-Holzmann I, Bruppacher R. Thromboembolic stroke in young women. *Contraception* 1998;57:29–37.
- [4] Lidegaard Ø, Kreiner S. Cerebral thrombosis and oral contraceptives. A case-control study. *Contraception* 1998;57:303–14.
- [5] Lidegaard Ø. Decline in cerebral thromboembolism among young women after introduction of low-dose oral contraceptives: an incidence study for the period 1980–1993. *Contraception* 1995;52:85–92.
- [6] Wermuth N, Lauritzen SL. Graphical and recursive models for contingency tables. *Biometrika* 1983;70:537–52.
- [7] Kreiner S. Analysis of multidimensional contingency tables by exact conditional tests. Techniques and strategy. *Scand J Stat* 1987;14:97–112.
- [8] Whittaker J. Graphical models in applied multivariate statistics. New York: John Wiley & Sons, 1990.
- [9] Glass R, Johnson B, Vessey M. Accuracy of recall of histories of oral contraceptive use. *Br J Prev Soc Med* 1974;28:273–5.
- [10] Stolley PD, Tonascia JA, Sartwell PE, et al. Agreement rates between oral contraceptive users and prescribers in relation to drug use histories. *Am J Epidemiol* 1978;107:226–35.
- [11] Rosenberg MJ, Layde PM, Ory HW, Strauss LT, Rooks JB, Rubin GL. Agreement between women's histories of oral contraceptive use and physician records. *Int J Epidemiol* 1983;12:84–7.
- [12] Coulter A, Vessey M, McPherson K. The ability of women to recall their oral contraceptive histories. *Contraception* 1986;33:127–37.
- [13] Lidegaard Ø. The influence of thrombotic risk factors when oral contraceptives are prescribed. A control-only study. *Acta Obstet Gynaecol Scand* 1997;76:252–60.
- [14] Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case-control study of migraine and risk of ischemic stroke in young women. *BMJ* 1995;310:830–3.
- [15] Lidegaard Ø. Thrombotic diseases in young women and the influence of oral contraceptives. *Am J Obstet Gynecol* 1998;179:S62–7.
- [16] Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993;306:956–63.