Oral contraceptives and venous thromboembolism: a five-year national case-control study☆

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Abstract

The objective of this study was to assess the influence of oral contraceptives (OCs) on the risk of venous thromboembolism (VTE) in young women. A 5-year case-control study including all Danish hospitals was conducted. All women 15–44 years old, suffering a first ever deep venous thrombosis or a first pulmonary embolism (PE) during the period January 1, 1994, to December 30, 1998, were included. Controls were selected annually, 600 per year in 1994–1995 and 1200 per year 1996–1998.

Response rates for cases and controls were 87.2% and 89.7%, respectively. After exclusion of nonvalid diagnoses, pregnant women, and women with previous thrombotic disease, 987 cases and 4054 controls were available for analysis.

A multivariate, matched analysis was performed. Controls were matched to cases within 1-year age bands. Adjustment was made for confounding influence (if any) from the following variables: age, year, body mass index, length of OC use, family history of VTE, cerebral thrombosis or myocardial infarction, coagulopathies, diabetes, years of schooling, and previous birth.

The risk of VTE among current users of OCs was primarily influenced by duration of use, with significantly decreasing odds ratios (OR) over time: <1 year, 7.0 (5.1–9.6); 1–5 years, 3.6 (2.7–4.8); and >5 years, 3.1 (2.5–3.8), all compared with nonusers of OCs. After adjustment for confounders, current use of OCs with second- (levonorgestrel or norgestimate) and third- (desogestrel or gestodene) generation progestins when compared with nonuse resulted in ORs for VTE of 2.9 (2.2–3.8) and 4.0 (3.2–4.9), respectively. After adjusting for progestin types and length of use, the risk decreased significantly with decreasing estrogen dose. With 30–40 μg as reference, 20 and 50 μg products implied ORs of 0.6 (0.4–0.9) and 1.6 (0.9–2.8), respectively ($p_{trend} = 0.02$). After correction for duration of use and differences in estrogen dose, the third/second-generation risk ratio was 1.3 (1.0–1.8; p <0.05).

In conclusion, use of OCs was associated significantly to the risk of VTE. The risk among current users was reduced by more than 50% during the first years of use. The risk increased more than 100% with increasing estrogen dose, and the difference in risk between users of third- and second-generation OCs, after correction for length of use and estrogen dose, was 33%. © 2002 Elsevier Science Inc. All rights reserved.

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1. Introduction

Through the last six years, hardly any epidemiologic issue has been so intensively investigated and debated as the influence of oral contraceptives (OCs) on the risk of venous thromboembolism (VTE; deep venous thrombosis (DVT) + pulmonary embolism; PE). Few are in doubt that OCs, in general, increase the risk of VTE. The controversy has been focused on a possible differential influence from OCs with different types of progestins, in particular whether OCs with second-generation progestins (levonorgestrel or norgestimate) confer less risk than do OCs with the third-generation progestins (desogestrel and gestodene). It has also been discussed which clinical implications such a difference should have. It is important to discriminate between these two issues because the former is a pure scientific issue to be resolved by skilled epidemiologists, the latter a clinical and political issue, to be resolved by a team of clinicians, epidemiologists, and health authorities.

From a scientific point of view, Denmark differs from other countries in Europe in several important aspects. First, we have a public health care system to which all people have free access.

Second, all Danish inhabitants have a specific personal

Table 1
Recent studies on low-dose oral contraceptives and venous thromboembolism

Study [reference]	Nationality	PDS*	Cases/controls	OR 2nd† 95% Cl	OR 3rd‡ 95% Cl
Bloemenkamp [1]	NL	88–92	126/159	3.8 1.7–8.4	8.7 3.9–19.3
WHO [2]	Europe	89–93	433/1044	3.6 1.4–7.9	8.7 3.9–19.3
Jick [3]	UK	91–94	80/cohort	1 reference	1.8 1.0–3.2
Spitzer [4]	Europe	91–95	471/1772	3.2 2.3–4.3	4.8 3.4–6.7
Lewis [17]	Europe	93–95	502/1864	2.9 1.9–4.2	2.3 1.5–3.5
Farmer [18]	UK	92–95	42/168	1 reference	0.7 0.4–1.6
Farmer [19]	UK	91–95	85/cohort	3.1 2.1–4.5	5.0 3.7–6.5
Lidegaard [5]	DK	94–95	375/1041	2.1 1.3–3.5	3.7 2.0–7.0
Todd [20]	UK	92–97	99/cohort	1 reference	1.4 0.7–2.8
Herings [21]	NZ	86–95	33/cohort	1 reference	4.2 1.7–10.2
Bloemenkamp [22]	NL	82–95	185/591	3.7 1.9–7.2	7.0 ?
Parkim [23]	NZ	90–98	17/25	5.1 1.2–21.4	14.9 3.5–64.3
Lidegaard [this study]	DK	94–98	987/4054	2.9 2.2–3.8	4.0 3.2–4.9

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

identification number, which is given at birth and which cannot be changed. These numbers are collected in the Central Person Register (CPR), which also includes actual addresses. This register is updated once every day. The majority of other registers in Denmark include these personal identification numbers. By using the CPR it is possible to establish random samples of women in specific age groups.

Third, we established in 1977 an electronic diagnosis registration system covering all hospitals (by law) through which all discharge diagnoses are collected centrally in the National Patient Register (NPR) with codes according to the World Health Organization's (WHO's) international classification of diseases (ICD). Since January 1, 1994, the ICD-X has been used in Denmark.

Fourth, specifically about the second-/third-generation pill controversy, Denmark also has special opportunities. A few days after the "Dear Doctor" letter[1] was sent out in UK in late 1995, the Danish Health Board (Sundhedsstyrelsen) sent out letters to all Danish general practitioners in which they indicated that they did not find any reason to change prescribing practice of OCs based on three circumstances: (1) the new studies (Table 1) [1–4] did not demonstrate risks of VTE higher than previously reported; (2) the differences suggested between second- and third-generation OCs could be influenced by prescription bias; and (3) there were scientific suggestions that third-generation OCs could confer less risk of arterial complications than could second-generation pills. The consequence was that the market share of third-generation OCs remained stable during the following five years and still is used by about two-thirds of the current users of OCs.

Fifth, there has been no media-storm on Danish television or in Danish newspapers on this issue during the last five years. And, finally, all young people suspected for VTE are referred to hospital. Therefore, hospital-based databases cover nearly all occurring VTE in the population.

According to ICD-X, VTE include the sub-diagnoses deep venous thrombosis I 80.1-I 80.3 and PE I 26. Specific codes exist for VTE during pregnancy.

A case-control study covering the five year period 1994–1998 with the aim to specifically explore the influence of different types of OCs on the risk of developing VTE is now completed. The results from the first two study years have previously been published [5]. This article presents the final results of the study. The results for acute myocardial infarction (AMI) and cerebral thrombosis have been submitted separately.

2. Material and methods

2.1. Cases

All Danish women 15–44 years old who suffered a VTE during the study period were included in the study. Women with VTE or other thrombotic diseases before 1994 (1980–1993) were identified in the register and primarily excluded from the study to include only first-ever events. Women who were registered more than once during the study 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, and time since last use of OCs among former users, smoking habits (never smokers, former smokers, 1–10 cigarettes/day, 11–20/day, >20/day), treated hypertension, current or previous pregnancy, treatment for hypertension in any previous pregnancy, previous thrombotic stroke, previous VTE, previous myocardial infarction, detected coagulation disturbances, hyperlipidemia, diabetes, heart diseases, recent surgery, presence of varicose veins, height and weight (body mass index; BMI), family history of specific thrombotic diseases, persisting clinical symptoms after VTE, length of schooling

(as a proxy for social class), diagnostic examinations conducted (ultrasound or venography for DVT, scintigraphic examinations for PE), anticoagulation treatment, 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 and age-matched to women with thrombotic stroke. During the period 1996–1998, 1200 women, 15–44 years old, were annually randomly selected from the CPR. By this design it was assured that the control group corresponded to the cases in terms of time (year) to account for changes in use of different types of OCs during the study period. Age differences between cases and controls were handled in the analysis by a one year age-matching.

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 one year after the VTE. 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 95247m). 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 VTE, 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 ethinyl estradiol (EE); 30–40 μg EE, including the sequential brands; pills with 20 μg EE, and progestin-only pills (POP).
II. Five groups according to progestin type: (a) estranes, including norethisterone, lynestrenol, ethynodiol, and 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, and >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) or 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 one 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 one 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 as well. Thus, to determine the isolated influence of the progestin type, 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. 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 differences 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 as these never-users of OCs could have special characteristics compared with ever-users, nonusers (never-users + former users) were used as the reference group. The assessment of the risk among former users of OCs was done with never-users of OCs as reference.

Table 2
Inclusion and exclusions of cases and controls

	Cases		Controls	
	Excluded	Remaining	Excluded	Remaining
Identified In	*NPR**	*1,660*	*CPR*	*4,800*
Non-Danish inhabitants	15	1,645	0	
Died since discharge	23	1,622	0	
Diagnosis not valid (information from dept.)	51	1,571	0	
Department closed	13	1,558	0	
No permission to contact	12	1,546	0	
Lack of permission to contact	96	1,450	0	
No available address/not at address	27	1,423	68	4,732
Submitted questionnaires (100%)		1,423		4,732
Returned questionnaires (response rate)	(87.2%)	1,241	(89.7%)	4,245
Previous VTE/thrombosis (information from case)	52	1,189	25	4,220
Invalid diagnosis (information from case)	95	1,094	0	4,220
Refuse invitation to participate	27	1,067	20	4,200
Pregnant	80	987	146	4,054
Included in analysis		987		4,054

* NPR = National Patient Register;

‡ CPR = Central Person Register.

3. Results

During the study period, 1660 women were identified in the NPR as alive at discharge from hospital (Table 2). Twenty-three women had died since discharge (mostly women with malignant diseases); in 51 women the diagnosis was uncertain (information from departments); for 12 women no permission to contact was given by the departments, primarily because of severe general/malignant disease; for 96 cases no response was achieved from the department; for 13 cases the department was closed; and 27 women had no available address or were not present at the address. Thus, 1423 questionnaires were submitted. One reminder was sent out to nonresponders within 3 months after the primary application.

We received 1241 (87.2%) questionnaires. All except 27 women agreed to participate. Of the remaining 1214 cases, 52 indicated previous VTE or other thrombotic disease, 80 that they were pregnant at the time of the attack (despite coded with the code for nonpregnant women), and 95 that they had an uncertain diagnosis. Thus, 987 women were available for analysis.

Of the 987 included cases, 309 (31%) had PE and 678 (69%) a deep venous thrombosis. The distribution of OC use in these two groups of cases did not differ significantly (56% and 51%, respectively). Consequently, all the cases were analyzed together.

Of 678 women with deep venous thrombosis, 361 (53%) had undergone venography, 317 (47%) had an ultrasound examination, and 656 (97%) had at least one of these examinations. Of the 678 women included, 634 (94%) had received anticoagulation therapy. Of the 22 women indicating no venography or ultrasound, 14 had received anticoagulation therapy. Three of the eight women with the least certain diagnosis were current users of OCs.

Of 309 women with PE (some of whom also had deep venous thrombosis), 292 (95%) had undergone scintigraphic examinations, 300 (97%) were anticoagulated, and 305 (97%) had at least one of these things. Thus, four women had an uncertain diagnosis of PE; three of whom, however, had a certain deep venous thrombosis.

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

3.1. OCs and VTE

Among the 987 women with VTE, 518 (52.5%) were current users of OCs, 11 (1.1%) were current users of cyproterone acetate (Diane Mite), 322 (32.6%) were former users, and 136 (13.8%) had never taken OCs. Among the controls, 1207 (29.8%) were current users of OCs; 2025 (50.0%) were former users, of these 38 (1%) were on cyproterone (Diane Mite); 713 (17.6%) never-users; and 71 (1.7%) nonspecified nonusers. The detailed distribution of current users of different types of OCs among cases and controls is given in Table 3. Of the 520 users of OCs who had had VTE, 495 (95%) could specify the brand taken. Among 1208 control users, 1186 (98%) could specify the brand. The 25 cases and 22 controls who did not specify the brand, as well as the women on cyproterone acetate, were not included in the multivariate analysis on differences between sub-types of OCs.

The crude age matched estimates (Table 4) demonstrated a decreasing risk by length of OC use, a higher risk for third- than for second-generation OCs, but no significant association to estrogen dose. After adjustment for BMI, years of schooling, coagulation disturbances, family VTE, family AMI, previous birth, diabetes, and smoking habits,

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

N (%)*	Estrans	Levonorgestrel	Norgestimate	Desogestrel	Gestodene	Total
Cases						
50 µg EE†	17 (3.4)	12 (2.4)	—	—	—	29 (5.9)
30–40 µg EE	19 (3.8)	86 (17.3)	18 (3.6)	63 (12.7)	206 (41.8)	392 (79.4)
20 µg EE	—	—	—	58 (11.9)	6 (1.2)	64 (13.1)
POP‡	8 (1.6)	0 (0.0)	—	—	—	8 (1.6)
Specified						493 (100)
Unspecified						25 (-)
Total						518
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)	952 (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.

minor changes in the crude trends were observed (Table 4). Family cerebral thromboembolic attack (CTA), hypertension, migraine, hyperlipidemia, and heart disease were all tested, but were without primary confounding influence or without further confounding influence after adjustment for the included confounders. The risk ratio between third- and second-generation OCs was 1.4 (1.1–1.9; p = 0.01) in the crude analysis and 1.4 (1.0–1.9; p = 0.04) in the adjusted analysis. Adjusted risk estimates for specific combinations of estrogen dose and progestin types are shown in Table 5.

When estrogen dose was corrected for differences in duration of use and progestin types, we found a significantly decreasing risk of VTE with decreasing estrogen dose (p = 0.02). The missing crude association between estrogen dose and risk of VTE, thus, was confounded by duration of use and the associated progestin type.

The difference observed between second- and third-generation OCs could be influenced by differences in duration of use in the two groups, to different estrogen doses combined with the two progestins, or to a different impact of the different progestins. To discriminate between these three possibilities, the risk estimate for third-generation OCs was adjusted according to duration of use and estrogen dose, so that the distribution was the same as for the reference group of second-generation users. These corrected estimates demonstrated OCs with third-generation progestins implying a 1.3 (1.0–1.8) times higher risk of VTE than OCs with second-generation progestins (p < 0.05; Table 4). Matching also for year did not change the estimate, 1.3 (1.0–1.8). And, finally, the trend in risk according to length of use was not weakened by correction for estrogen dose and progestin types, nor by adjustment for any of the involved confounders, p < 0.01.

In conclusion, the risk of VTE among current users of OCs was primarily influenced by length of use, secondly by the estrogen dose, but also significantly by the progestin type. According to this study, OCs with 50 µg EE increased the risk of VTE 4.2 times, middle-dose OCs with 30–40 µg EE combined with second-generation progestins increased the risk 2.9 times, whereas middle- and low-dose (20 µg EE) OCs with the third-generation progestins desogestrel or gestodene conferred a four times increased risk of VTE. POPs did not confer any significant increase in the VTE risk, despite a point estimate of 2.0 (0.8–5.1; p = 0.14).

3.2. Other risk factors

Smoking less than 10 cigarettes/day did not increase the risk of VTE. More than 10 cigarettes/day increased the risk 71%, and more than 20/day increased the risk 94% (Table 6).

Family VTE increased the risk three times, whereas cerebral thrombosis or myocardial infarction in one or both parents did not confer any increased risk of VTE.

BMI was significantly associated with the risk of VTE, with women with BMI >30 having a five times increased risk of VTE (Table 6). Hypertension, diabetes, previous birth, migraine, and hyperlipidemia did not increase the risk of VTE significantly.

Women with coagulation disturbances had an adjusted risk of VTE of 37.4 (19.3–72.6). The risk of VTE decreased significantly with increasing length of schooling (Table 6). Compared with women with 7–9 years of schooling, women with 11–12 years had a 58% (0.34–0.54) decreased risk of VTE.

Table 4
Risk of venous thromboembolism in users of different types of OCs

	Cases/controls n/n	Crude*		Adjusted[†]		Corrected[‡]	
		OR	95% Cl	OR	(95% Cl)	OR	(95% Cl)
Never use	136/713	1 (reference)		1 (reference)			
Former use	322/2,025	0.6	0.5–0.7	0.6	0.4–0.7		
Nonuse[§]	458/2,738	1 (reference)		1 (reference)			
Current use	518/1,208						
Duration of use (years)							
<1	124/173	7.0	5.2–9.3	7.0	5.1–9.6	1 reference	
1–5	137/412	3.3	2.6–4.3	3.6	2.7–4.8	0.5	0.4–0.8
>5	229/596	2.8	2.3–3.4	3.1	2.5–3.8	0.5	0.3–0.7
Generation							
First-generation	29/46	3.7	2.3–6.2	4.1	2.4–7.1	1.5	0.9–2.7
Second-generation	104/300	2.6	2.0–3.4	2.9	2.2–3.8	1 reference	
Third-generation	333/735	3.7	3.0–4.5	4.0	3.2–4.9	1.3	1.0–1.8
Estrogen dose							
50 μg EE	29/46	3.7	2.3–6.2	4.2	2.4–7.1	1.6	0.9–2.8
30–40 μg EE	392/953	3.2	2.7–3.8	3.4	2.8–4.2	1 reference	
20 μg EE	64/159	3.8	2.5–5.1	4.3	2.9–6.2	0.6	0.4–0.9
POP	8/28	1.6	0.7–3.6	2.0	0.8–5.1	—	
Progestin type							
Estrans	36/107	2.6	1.7–3.6	2.9	1.8–4.6	0.7	0.4–1.1
Levonorgestrel	98/198	3.2	2.4–4.3	3.6	2.6–4.9	1 reference	
Norgestimate	18/118	1.4	0.8–2.5	1.7	1.0–3.2	0.4	0.2–0.8
Desogestrel	121/219	4.2	3.2–5.6	5.1	3.8–6.9	1.6	1.0–2.4
Gestodene	212/516	3.4	2.7–4.2	3.5	2.7–4.4	1.0	0.7–1.4

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

[†] Adjusted for age, year, family VTE, BMI, years of schooling, smoking, diabetes, coagulation disturbances, and previous birth. Variables without confounding influence, or with no confounding influence after adjustment for the included confounders: hypertension, heart disease, family CTA, migraine, hyperlipidemia.

[‡] Generation: corrected for differences in duration of use. Estrogen dose: corrected for duration of use and progestin types. Progestin type: corrected for duration of use and estrogen dose.

[§] Nonuse = former use + never use.

3.3. Interaction and effect modification

There was generally no interaction or effect modification between the identified 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 for the separate risk factors.

4. Discussion

4.1. Validity of diagnoses

Four attempts were made to ensure the validity of the diagnoses. First, all the cases were identified in the NPR, which is based on doctors' discharge diagnoses from the

Table 5
Adjusted risk estimates* of venous thromboembolism 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[†]	3.6	5.3	—	—	—	—
	1.8–7.1	2.3–12.3	—	—	—	—
30–40 μg EE	2.5	3.4	1.7	5.4	3.5	3.3
	1.4–4.5	2.5–4.7	1.0–3.1	3.6–8.0	2.8–4.5	1.4–7.6
20 μg EE	—	—	—	4.8	2.0	—
	—	—	—	3.2–7.1	0.7–5.7	—
POP	2.0	—	—	—	—	—
	0.8–5.1	—	—	—	—	—

* The adjusted estimates are not corrected for differences in length of use in the different categories of users of specific types of OCs.

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

Table 6
Influence from other risk factors on the risk of VTE

Risk factor	Cases	Controls	Crude OR[†]	Adjust OR[‡]	95% CI
Smoking[1]	n (%)	n (%)			
Never smokers	338 (34.2)	1,699 (42.0)	1	1	Reference
Former smokers	140 (14.2)	786 (19.4)	0.9	1.0	0.8–1.3
1–10 per day	146 (14.8)	576 (14.2)	1.2	1.3	1.0–1.6
11–20 per day	265 (26.8)	755 (18.7)	1.7	1.7	1.4–2.1***
>20 per day	100 (10.1)	230 (5.7)	2.0	1.9	1.4–2.7***
BMI[2]					
10–20	167 (17.4)	994 (24.8)	1	1	Reference
21–25	411 (42.8)	2,166 (54.0)	1.1	1.1	0.9–1.4
26–30	209 (21.8)	651 (16.2)	1.9	1.9	1.5–2.5***
>30	173 (18.0)	204 (5.1)	5.2	5.1	3.8–6.9***
Hypertension[3]	30 (3.0)	58 (1.4)	1.9	1.5	0.9–2.6
Migraine[4]	69 (7.0)	258 (6.4)	1.1	1.0	0.7–1.3
Diabetes[5]	2 (0.2)	15 (0.4)	0.4	0.3	0.1–1.2
Family AMI[6]	157 (15.9)	520 (12.8)	1.2	1.1	0.8–1.3
Family CTA[7]	59 (6.0)	239 (5.9)	1.0	0.8	0.5–1.0
Family VTE[8]	144 (14.5)	193 (4.8)	3.2	3.0	2.3–4.0***
School[9] (years)					
7–9	273 (27.6)	590 (14.6)	1	1	Reference
10	356 (36.0)	1,339 (33.1)	0.5	0.6	0.5–0.8***
11–12	360 (36.4)	2,118 (52.3)	0.3	0.4	0.3–0.5***
Hyperlipidemia[10]	17 (1.7)	24 (0.6)	2.9	1.9	0.9–3.9
Coag. disturb.[11]	86 (8.7)	12 (0.3)	36.7	37.4	19.3–72.6***
Previous birth[12]	603 (60.9)	2,324 (57.3)	1.1	0.9	0.8–1.2

* p < 0.05; ** p < 0.01; *** p < 0.001.

[†] Crude: Matched for age and year.

[‡] Adjusted for final set of confounders which were:

[1] OC use, BMI, years of schooling.

[2] Age, year, OC use, smoking, coagulation disturbances, years of schooling, family VTE.

[3] Age, BMI, years of schooling, family VTE, diabetes.

[4] OC use, years of schooling, BMI.

[5] OC use, hypertension, hyperlipidaemia.

[6] Age, OC use, BMI, family VTE, hypertension.

[7] Age, BMI, family VTE, family AMI.

[8] Age, OC use, years of schooling, family AMI, hypertension.

[9] Age, year, OC use, smoking, BMI, family VTE, previous birth, hypertension, migraine.

[10] Family VTE, diabetes, years of schooling, coagulation disturbances.

[11] OC use, BMI, hyperlipidemia.

[12] Age, OC use, years of schooling, smoking, family AMI.

involved departments. Second, 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. Third, each woman included in the analysis confirmed her own diagnosis. And fourth, a very high percentage of cases had their diagnosis confirmed by a venography, ultrasound, or scintigraphic examinations and were anticoagulated. For these reasons, the diagnoses included in the final analysis seem for a very high percent to represent true VTE.

4.2. Validity of exposures

Women generally have a fair recall of their contraceptive habits [10–13]. About one year after the event, the cases were asked about their use of OCs at the time of their admission to hospital. Both cases and controls were given a list of available brands of OCs with the questionnaire. Ninety-five 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 the fact that only 2% of the control woman did not specify the brand taken.

We have been criticized for our design [14]. The claim has been that the cases were asked about their OC use at admittance to hospital about one year after the event, whereas we established control groups in each of the study years, and they indicated their use/nonuse of OCs at the time they received the questionnaires, thereby potentially introducing a differential recall between cases and controls [14]. We have replied that we attempted to reduce the recall bias as much as practically possible by asking the controls about

their actual use of OCs (thereby reducing any recall bias to a minimum) [15]. Because of the practice in the NPR, we were not able to catch the women with VTE before about one year after their attack. Therefore, we could not have reduced their recall period of about one year further. There is, however, an important difference between cases and controls. The cases have an event (their VTE) to which they can link their recall of OC use. A VTE is not a daily event, and all women suffering a VTE will have had speculations about any possible causes. The hospital staff will have asked nearly all the cases about any use of OCs when they were admitted to hospital. Therefore, recall bias among cases is not very likely. If we alternatively (as has been suggested) had asked the controls about their use of OCs one year before (thereby making the recall period equal for cases and controls), we would have had a good chance of introducing a differential recall between cases and controls, because the controls do not have any event to which they can link their use of OCs one year ago. Therefore, we are still of the opinion that a differential recall bias in this study is unlikely, and that our design, if anything, ensures the smallest possible recall bias.

4.3. Selection of controls

Controls were selected at random from the CPR. During the first two study years, the controls were age-matched to cases with thrombotic stroke [5]. To increase the statistical power in the young age groups with the majority of OC users, but where thrombotic diseases are rare events, we increased the number of controls per year from 600 to 1200 during the last three study years and made a flat age-distribution of these controls. Therefore, it was necessary to make a matched analysis of data in which the controls were matched to cases within one year age bands and according to calendar year.

4.4. 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 87% and 90%, respectively, implies that response-selection probably had little influence in this study.

4.5. 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 at an anticipated increased thrombotic risk [16]. 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 venous thromboembolism, BMI, smoking, and years of schooling are probably the most important confounders to adjust for to account for prescribing bias. All these variables were included in the multivariate analysis, and adjustment for these confounders did not confer significant changes in the risk estimates.

4.6. 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 VTE than nonusers of OCs. If any such selection is in effect, the risk of OCs is overestimated. Whereas the overall risk figure for OCs cannot be excluded to be overestimated, the difference between subtypes of OCs, on the other hand, is not likely to be influenced by referral bias.

4.7. Evaluation of results

There is a good agreement between different studies that use of OCs increases the risk of VTE several times. In several recent studies, no significant association between risk of VTE and estrogen dose could be demonstrated [2,4]. It is interesting that our crude estimates did not demonstrate any dose-response relationship. The adjusted estimates did not demonstrate a convincing relationship. However, after correction for progestin types and length of use, a very clear dose-response relationship between estrogen dose and risk of VTE was demonstrated. The explanation is primarily that many users of older, high-dose pills have taken the pills for many years and, secondly, that they contain older progestin types. In the reanalysis of the Transnational Study that included full exposure history [17], the influence of estrogen dose was more apparent than in the primary publication [4].

OCs with second-generation progestins have been demonstrated to increase the risk two to five times (Table 1). It is more controversial how much the risk of VTE is increased among users of third-generation OCs because the ORs range from 2.3 to 14.9. Except for the reanalysis of the Transnational study database [17], and a study of German women [18], all studies have demonstrated a higher risk of VTE for third- compared with second-generation pills, with third- to second-generation risk ratios ranging from 1.3 to 4.2.

In this study, confounder control for family VTE, BMI, and coagulation disturbances only reduced the third- to second-generation risk ratio a little, and less than in our primary analysis of the first two study years. The explanation probably is, first, that the cases and controls were more closely matched in our final analysis; second, that some Danish prescribers of OCs do not any longer consider third-generation OCs as more safe concerning cardiovascular complications, as many did five years ago. Preferential

prescribing, therefore, is not apparent in Denmark any longer. Some physicians may, during the latest years, have changed their practice in light of the new epidemiologic data. That circumstance does not invalidate our data because we controlled for the relevant confounders (family VTE, BMI, and years of schooling) in this respect. Furthermore, the overall proportion of sold OCs with third-generation progestins has not decreased during the last five years in Denmark.

The difference in length of use between users of second- and third-generation OCs was also less dominant during the last three study years than in the first two study years, probably a simple consequence of third-generation OCs being introduced in Denmark about 10 years ago, and many women, therefore, have now also taken third-generation pills for many years.

Our third- to second-generation risk ratio of 1.3 is close to the ratio found in several recent studies [4,19,20]; it is smaller, however, than in most other studies [1,2,3,21–23].

Although there is actual controversy about the trend in the VTE incidence rates in the UK after the change from third- to second-generation pills in 1995 [24,25], with the introduction of third-generation OCs in late 1980s, there was a 17% increase in the incidence of VTE among young women in Denmark that was not seen in men during the same period [26]. Although pregnant women had an increase in VTE of 150% through the same years [27], the many epidemiologic contributions through the last five years makes it scientifically plausible that a real difference in the risk of VTE exists between users of second- and third-generation OCs. Close age-matching and careful adjustment for length of use seems to be important methodological conditions to account for. The high risk estimates in some studies could be due to insufficient control for these two confounders.

Although a scientific agreement is approaching, there is still discussion concerning the clinical impact of the epidemiologic findings. In the general evaluation of thrombotic risks, it should not be necessary any longer to repeat that we have to consider venous as well as arterial complications, relative as well as absolute risks, the case-fatality rate for each diagnosis, and (which is often forgotten) the consequences of the disease for the survivors of VTE [9,28].

In women under 30 years of age, the incidence rate of VTE and thrombotic stroke is 10/ and 3/100,000 per year, respectively [9]. In women 30–44 years old, the incidence rate is 23 and 15/100,000 women, respectively. The mortality in the two age groups is 0.6 and 1.7 per million for VTE and 2.2 and 2.3 per million for cerebral thrombosis. About 5% of women with VTE have significant disability after their attack versus 30% of women with stroke. In conclusion, VTE in young women is more frequent, but with a lower mortality and disability than in young women with thrombotic stroke.

The WHO study [29], our primary publication [30], as well as our final analysis (submitted), all suggest a 40–50%

lower risk of CTA in users of OCs with third- compared with second-generation progestins. On the other hand, there is no convincing evidence of a differential risk of AMI according to progestin types.

Our tentative clinical recommendation, therefore, is if women with family VTE (mother, sister, or brother), with high BMI, or with genetic predisposition of VTE are prescribed OCs, a natural first choice would be a low-dose pill with a second-generation progestin. If women with family history of stroke (mother, sister, or brother), who smoke cigarettes, have controlled hypertension, who have migraine or are over 35 years in age are prescribed OCs, a natural first choice would be a low-dose pill with a third-generation progestin. For women at a particular high risk of thrombosis, alternative contraceptive methods should be considered. Young women without predispositions could take any low-dose pill safely.

4.8. Other risk factors

Smoking has an impact on the risk of VTE if women smoke more than 10 cigarettes/day. However, the influence on VTE is smaller than the influence on cerebral thrombosis and in particular on AMI.

The increasing risk of VTE with increasing BMI has been found in several previous studies. Likewise, more education, not surprisingly, also implies a reduced risk of venous thrombosis.

VTE in a close relative increased the risk of VTE three times. That circumstance still makes it meaningful to ask all women at prescription of OCs about any such disposition. AMI and cerebral thrombosis in the family did not confer any increased risk of VTE, which is in accordance with the pathogenesis of arterial and venous diseases being quite different.

The high OR of VTE among women with coagulation disturbances is undoubtedly exaggerated. Women who have had a venous thrombotic event are often examined for coagulation disturbances, which are found in a high percentage of these women. The controls, on the other hand, have never had an event that would lead to a coagulation screening, despite that several percent of "normal" women have such factors. Unfortunately, we have no possibility of adjusting for this ascertainment bias.

The classic arterial risk factors, hypertension, diabetes, hyperlipidemia, and migraine did not confer any significantly increased risk of VTE according to our data, findings that further support another pathogenesis for venous diseases than for arterial thrombosis.

5. Conclusion

In young women, 1–3/10,000/year experience a venous thrombosis. Genetic predisposition increases the risk 5–10 times. Pregnancy and severe obesity increase the VTE risk

five times, low-dose third-generation OCs four times, low-dose second-generation OCs and family disposition three times, whereas smoking and moderate adiposity imply ORs of below 2. The case-fatality rate in young nonpregnant women is below 1%.

Note

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

Acknowledgment

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