

Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) Study

Oral Contraceptives and the Risk of Ischemic Stroke

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Background and Purpose—Epidemiological studies have shown an increased risk of venous thrombosis in women taking third-generation oral contraceptives, ie, those containing the progestogens desogestrel or gestodene. This study assesses the risk of ischemic stroke with several types of oral contraceptives.

Methods—A multicenter, population-based, case-control study was performed in 9 Dutch centers in women aged 18 to 49 years. Women with a first ischemic stroke were compared with control women without vascular diseases. The control subjects were recruited by random-digit dialing and were stratified by age, area of residence, and year of stroke. All patients and control subjects filled in a questionnaire about the use of oral contraceptives and risk factors for ischemic stroke. Odds ratios were adjusted for the stratification factors.

Results—Two hundred three women with an ischemic stroke and 925 control women were included. The risk of stroke in women using any type of oral contraceptives versus none was 2.3 (95% CI 1.6 to 3.3). Current users of first-generation oral contraceptives had an odds ratio of 1.7 (95% CI 0.7 to 4.4). Low-dose second-generation oral contraceptives increased the risk of stroke 2.4 times (95% CI 1.6 to 3.7), and third-generation oral contraceptives increased the risk of stroke 2.0 times (95% CI 1.2 to 3.5). The risk of stroke in women using third-generation oral contraceptives was not different from that in women using second-generation oral contraceptives (odds ratio 1.0, 95% CI 0.6 to 1.8).

Conclusions—Third-generation oral contraceptives (containing desogestrel or gestodene) confer the same risk of first ischemic stroke as second-generation oral contraceptives (containing levonorgestrel). (*Stroke*. 2002;33:1202-1208.)

Key Words contraceptives, oral ■ epidemiology ■ estrogens ■ progestins ■ stroke, ischemic

Stroke is rare in young women. Approximately 50% to 70% of these events are embolic.¹ The first report on the occurrence of stroke in women using oral contraceptives was published in 1962,² followed by many others.³⁻⁵ Acute myocardial infarction and deep venous thrombosis were also linked to oral contraceptive use.^{3,6,7} Efforts to decrease the risk of arterial thrombosis led to the development of oral contraceptives containing <50 µg ethinylestradiol and the development of other progestogens, ie, levonorgestrel (second-generation oral contraceptives). Oral contraceptives containing a so-called third-generation progestogen (gestodene or desogestrel) were introduced in the 1980s. They appeared to be less androgenic than older products, and they tended to increase HDL cholesterol

levels.^{8,9} It was hypothesized that these oral contraceptive pills might reduce the risk of arterial thrombosis.^{9,10}

In 1995, several articles reported that users of third-generation oral contraceptives had an at least 2-fold increased risk of venous thrombosis.¹¹⁻¹⁴ More recently, a similar increase was reported for venous sinus thrombosis.¹⁵ These findings led to the discussion about the safety of these pills. If users of third-generation oral contraceptives suffer less from arterial thrombosis, this could counterbalance the venous thrombosis risk, and differential prescription according to risk factors could be desirable.

Studies involving a possible differential effect by third-generation oral contraceptives have been conflicting regard-

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Dr Kemmeren and Dr Algra participated in a study about the effect of second- and third-generation oral contraceptives on hemostasis. This study was sponsored by the Netherlands Thrombosis Foundation with money they had received for studies of this purpose from Organon, Oss. This construction was made to guarantee independence. Dr Helmerhorst supervised studies sponsored or assigned by various pharmaceutical companies that manufacture oral contraceptives but not studies on the relative merits of third- versus second-generation contraceptives.

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ing the risk of ischemic stroke.^{16–19} We conducted a case-control study among young women in the Netherlands to assess the effect of current combined oral contraceptives on the risk of ischemic stroke. We focused on the dose of estrogen and type of progestogen.

Subjects and Methods

Study Design

The Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study is a multicenter, population-based, case-control study. The study consists of 3 substudies for vascular events (ischemic stroke, myocardial infarction, and peripheral vascular disease) during oral contraceptive use in the Netherlands. The results for myocardial infarction^{19a} and peripheral vascular disease are reported separately. The study was approved by the ethics committees of the participating hospitals (see Appendix). All participants gave informed consent.

Identification of Women With Ischemic Stroke

Records were reviewed for ischemic stroke in 9 Dutch centers. Eligible patients were women aged 19 to 49 years who were hospitalized for a first ischemic stroke between January 1990 and October 1995. The end date was the publication time of 4 studies associating third-generation oral contraceptives with venous thrombosis.^{11–14} As a consequence of these articles, changes in the prescription of oral contraceptives by general practitioners that could influence the results of the study may have occurred.

Ischemic stroke was diagnosed on the basis of medical history, neurological examination, and CT or MRI scan by experienced neurologists in the participating centers. Exclusion criteria were transient ischemic attack (an event lasting <24 hours), hemorrhagic stroke, venous sinus thrombosis, carotid artery dissection, history of cardiovascular or cerebrovascular diseases, severe illness, aphasia, or cognitive impairment interfering with the questionnaire or not speaking Dutch.

Of the 295 eligible patients admitted during the study period, 18 died after stroke. Of the remaining 277 patients, 23 could not be located despite extensive efforts, and 24 women refused to participate. The overall response was 203 (69%) of 295 patients.

Control Women

This project included 3 types of arterial disease, ie, ischemic stroke, myocardial infarction, and peripheral arterial disease. We proceeded to include 1 large control group to which each of the 3 groups of patients was contrasted. The population-based group of control women was identified by random-digit dialing.^{20–22} In this method, private telephone numbers are randomly produced, which are subsequently dialed during all times of day, including the weekend; each number is dialed at least 7 times or until a successful connection is made. We reached 97.5% percent of the numbers after 15 725 telephone calls. Households were ascertained for eligible (age, sex) individuals who were subsequently asked to participate. Eligible for controls were women who were aged 18 to 49 years and who did not meet the exclusion criteria that were used for selecting patients with an ischemic stroke. Because age, area of residence, and calendar year were potential confounding factors, we wished to be able to adjust for these variables as efficiently as possible. The control women were recruited from the same geographic areas as the women of the 3 patient groups combined (6 areas of residence widely distributed over the country), and control questionnaires were assigned an index year corresponding to the event years of the 3 patient groups combined (1990 to 1995). Therefore, a control woman received 1 of the 6 questionnaires for 1 of the index years 1990 to 1995, and all questions elicited information from a time period preceding the index date. As the index date, we used the date of the stroke in the patients, and the midyear in control women. Finally, in random-digit dialing for control subjects, women in the older age groups were over-sampled to minimize the age difference between the patients and the

control women; this was accomplished by increasing the lower age limit of the eligibility criteria during the final months of control recruitment. Therefore, the control group may be seen as a sample of the population that is stratified by age, area of residence, and calendar year; therefore, adjustment for these factors is appropriate.

A total number of 1259 women were reached by random-digit dialing. Questionnaires were sent to 1039 women who were eligible as controls and who were free of a personal history of coronary heart disease, cerebrovascular disease, and peripheral artery disease. A total of 925 questionnaires were returned (73%).

Data Collection

Patients and control women received a standardized mail questionnaire involving demographic, medical, and reproductive history; use of oral contraceptives, along with specific brand used and previous use of oral contraceptives; family history of vascular diseases; smoking status; education level; history of hypertension, diabetes, and hypercholesterolemia; weight and height; and history of migraine. Color photographs of boxes of all oral contraceptive pills marketed in the Netherlands were used to help women recall the specific brand of oral contraceptives used. Questionnaires were mailed to the women with an ischemic stroke and to the control women between June 1996 and June 1999.

Current use of oral contraceptives was defined as use of an oral contraceptive within 1 month before the index date. Nonuse was defined as past use or no past use. Oral contraceptives were divided into 4 groups according to the type of progestogens: (1) first-generation oral contraceptives, containing lynestrenol or norethindrone; (2) second-generation oral contraceptives, containing norgestrel or levonorgestrel; (3) third-generation oral contraceptives, containing desogestrel or gestodene; and (4) oral contraceptives containing other types of progestogens (ie, norgestimate, cyproterone acetate, and medroxyprogesterone acetate [used in progestogen-only preparations]). Smoking was defined as having smoked in the year before the index date. A history of hypertension, diabetes, hypercholesterolemia, and migraine was based on a self-reported physician's diagnosis or medication use before the index date. Body mass index was calculated as self-reported body weight (in kilograms) divided by self-reported height squared (in meters squared). We considered women with a body mass index ≥ 27.3 kg/m² to be obese.^{23,24} Alcohol use in the period before the index date was categorized into 3 classes: never, 1 to 15 drinks a week, and >15 drinks a week. Family history of cardiovascular diseases was defined as the presence of vascular diseases among the parents or sibling(s) aged <60 years.

Statistical Analysis

Univariate odds ratios (ORs) were calculated for the relationship between type of oral contraceptives and the case-control status. ORs and 95% CIs were calculated by unconditional logistic regression and were adjusted for the stratification variables, ie, age, area of residence, and calendar year. In multivariate analysis, putative confounders for ischemic stroke²⁵ were included in the model, ie, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and alcohol use. To exclude an effect of estrogen dose in the analysis focused on type of progestogens, we excluded oral contraceptives not containing 30 μ g ethinylestradiol: 24 women who used oral contraceptives containing 50 μ g ethinylestradiol, 66 women who used second-generation triphasic oral contraceptives, 19 women who used 20 μ g ethinylestradiol, and 3 women who used third-generation triphasic oral contraceptives. Seventeen women used combined oral contraceptives for which the amount of ethinylestradiol was unknown. Similarly, to assess the effect of estrogen dose, we restricted the analysis to preparations containing the progestogen levonorgestrel. In a further effort to exclude all possibilities of confounders, in particular by preexisting disease, we repeated the analysis after excluding subjects with major cardiovascular risk factors. Stratum-specific ORs for major risk factors for ischemic stroke were obtained to assess whether the risk of stroke with oral contraceptive use differs among women with and without these characteristics.

TABLE 1. Baseline Characteristics of Young Women With a First Ischemic Stroke and Control Women

| | Stroke Patients (n=203) | Control Women (n=925) |
|---|----------------------------|--------------------------|
| Age, y | 39.3±8.3 | 38.1±8.3 |
| White ethnicity, n (%) | 188 (93) | 864 (93) |
| Education level, n (%) | | |
| Primary school or less | 92 (45) | 278 (30) |
| Secondary school | 81 (40) | 390 (42) |
| Higher education or university | 25 (12) | 252 (27) |
| History of hypertension, n (%) | 48 (24) | 56 (6) |
| History of hypercholesterolemia, n (%) | 10 (5) | 24 (3) |
| History of diabetes, n (%) | 11 (5) | 13 (1) |
| History of migraine, n (%) | 8 (4) | 18 (2) |
| Body mass index | 24.3±5.6 | 23.5±3.9 |
| Cigarette smoking, n (%) | | |
| Never | 44 (22) | 305 (33) |
| Former | 33 (16) | 222 (24) |
| Current | 126 (62) | 394 (43) |
| Alcohol use, n (%) | | |
| Never | 86 (43) | 287 (31) |
| 1–15 glasses a week | 112 (55) | 592 (65) |
| >15 glasses a week | 4 (2) | 39 (4) |
| Family history of cardiovascular disease, n (%) | 97 (48) | 311 (34) |

Values are mean±SD or number (percentage) of individuals.

In the remainder of the text, all ORs are adjusted for the stratification factors age, area of residence, and calendar year, unless additional adjustment is mentioned.

Results

Table 1 summarizes the characteristics of 203 women with ischemic stroke and 925 control women. The age of the patients varied from 19 to 49 years, and the age of the control women varied from 18 to 49 years. Compared with control subjects, patients had a lower education level, more often smoked cigarettes, and more often reported a history of hypertension, hypercholesterolemia, diabetes, migraine, or family history of cardiovascular disease.

Table 2 shows the frequency of oral contraceptive use in women with and without a stroke. Fifty percent of the patients versus 38% of the control subjects used some type of oral contraceptive. Compared with control women, patients more frequently used second- and third-generation oral contraceptives.

The risk of stroke in women currently using any type of oral contraceptive compared with nonusers was increased 2-fold (OR 2.3, 95% CI 1.6 to 3.3, adjusted for the stratification factors). After additional adjustment for potential confounders (hypertension, diabetes mellitus, hypercholesterolemia, smoking, and alcohol), the OR was essentially the same. Restricting the analysis to women without these cardiovascular risk factors showed an increased risk of 3.2 (95% CI 1.5 to 6.6). We observed little effect of oral contraceptives among the youngest women (<30 years), whereas the risk is

TABLE 2. OC Use in Women With First Ischemic Stroke and Control Women

| | Stroke Patients (n=203) | Control Women (n=925) |
|--|----------------------------|--------------------------|
| Current OC use, n (%) | | |
| All types | 102 (50) | 348 (38) |
| First-generation OC (lynestrenol or norethindrone) | 7 (3) | 31 (3) |
| Second-generation OC (levonorgestrel*) | 52 (26) | 173 (19) |
| Third-generation OC (desogestrel or gestodene) | 32 (16) | 110 (12) |
| Other† | 9 (5) | 28 (3) |
| Type unknown | 2 (1) | 6 (1) |
| Noncurrent OC use, n (%) | 101 (50) | 568 (61) |
| Use unknown, n (%) | 0 | 7 (1) |
| Hormone replacement therapy, n (%) | 0 | 2 (0) |

OC indicates oral contraceptive. Values are number (percentage) of individuals.

*Among patients and controls, no women used a second-generation OC containing the progestogen norgestrel.

†Including OCs containing cyproterone, norgestimate, and progestogen only.

2- to 3-fold increased among women aged >30 years (Table 3). Additional adjustment for potential confounders did not affect these results.

Women who used first-generation oral contraceptives (7 patients and 31 control subjects) had a 1.7-fold increased risk of stroke compared with stroke risk in women who did not use oral contraceptives (95% CI 0.7 to 4.4, Table 4). Compared with nonusers, the OR for stroke in women who used second-generation oral contraceptives containing levonorgestrel was 2.4 (95% CI 1.6 to 3.7), and for women on third-generation oral contraceptives containing desogestrel or gestodene, it was 2.0 (95% CI 1.2 to 3.5). The risk for third-generation oral contraceptives was not different from that for second-generation oral contraceptives (OR 1.0, 95% CI 0.6 to 1.8) and did not change after additional adjustment for putative confounding factors for ischemic stroke. When we restricted these analyses to users of second-generation oral contraceptives and third-generation oral contraceptives that contained 30 µg ethinylestradiol, the ORs did not change substantially: 1.5 for users of first-generation oral contraceptives (95% CI 0.5 to 4.4), 2.4 for users of second-generation

TABLE 3. ORs (95% CI) for Women With First Ischemic Stroke in Relation to OC Use (All Types) by Age Categories

| Age Category | Current OC Use/Noncurrent OC Use | | OR (95% CI)* |
|----------------|----------------------------------|---------------------------|---------------|
| | Stroke Patients (n=203) | Control Women (n=925)† | |
| 18–29 y, n (%) | 30/7 (81) | 145/42 (78) | 1.3 (0.5–3.3) |
| 30–39 y, n (%) | 31/21 (60) | 123/184 (40) | 2.3 (1.2–4.3) |
| 40–49 y, n (%) | 41/73 (36) | 80/342 (19) | 2.6 (1.6–4.2) |

Values are number (percentage using an OC) of individuals.

*Adjusted for stratification factors (area of residence and calendar year).

†Nine control women were left out of the analysis: OC use was unknown in 7 women, and 2 women used hormone replacement therapy.

TABLE 4. ORs (95% CI) for Ischemic Stroke in Relation to Different Types of Progestogens*

| | OR* (95% CI) | Adjusted OR† (95% CI) |
|---|-----------------|--------------------------|
| Any current OC use | 2.3 (1.6–3.3) | 2.1 (1.5–3.1) |
| First-generation OC use (lynestrol of norethindrone) | 1.7 (0.7–4.4) | 1.8 (0.7–4.7) |
| Second-generation OC use (levonorgestrel)‡ | 2.4 (1.6–3.7) | 2.1 (1.3–3.3) |
| Third-generation OC use (desogestrel or gestodene) | 2.0 (1.2–3.5) | 2.3 (1.3–4.2) |
| Other§ | 2.0 (0.8–4.8) | 1.5 (0.6–4.0) |

ORs are relative to nonusers: 101 patients and 568 control women.
 *Adjusted for stratification factors (age, area of residence, and calendar year).
 †Adjusted for stratification factors, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and alcohol use.
 ‡Among patients and controls, no women used a second-generation OC containing the progestogen norgestrel.
 §Including OCs containing cyproterone, norgestimate, and progestogen only.

oral contraceptives (95% CI 1.4 to 4.1), and 2.2 for users of third-generation oral contraceptives (95% CI 1.2 to 3.9). A direct comparison of third- and second-generation oral contraceptives containing 30 µg ethinylestradiol revealed an OR for stroke of 1.1 (95% CI 0.5 to 2.1). For women without any cardiovascular risk factors, we found an OR of 3.9 (95% CI 1.2 to 12.4) for second-generation oral contraceptive use versus no use and 4.6 (95% CI 1.7 to 12.8) for third-generation oral contraceptive use versus no use, with both containing 30 µg ethinylestradiol.

Use of oral contraceptives with estrogen doses of ≥50 µg (irrespective of the progestogen content) versus no use was associated with an OR for stroke of 3.1 (95% CI 1.2 to 7.9). This was slightly higher than the OR of preparations with <50 µg estrogen (OR 2.3, 95% CI 1.5 to 3.4). In a direct comparison of preparations (doses of <50 versus ≥50 µg ethinylestradiol), the OR was 0.8 (95% CI 0.3 to 2.3). These results were essentially the same after additional adjustment for risk factors for stroke. To evaluate the effect of ethinylestradiol dose without the influence of the accompanying progestogen, we restricted the analysis to oral contraceptives containing the progestogen levonorgestrel (Table 5). Users of oral contraceptives with 50 µg ethinylestradiol (and 125 µg levonorgestrel) had a risk of 2.7 (95% CI 1.0 to 7.6) compared with nonusers. Almost the same result was found in

users of oral contraceptives with 30 µg ethinylestradiol (and 150 µg levonorgestrel; OR=2.4, 95% CI 1.4 to 4.1). In a direct comparison, we found an OR of 0.7 (95% CI 0.2 to 2.5).

Table 6 shows the ORs of any oral contraceptive use according to the presence or absence of risk factors for ischemic stroke. In nonusers, the risk of stroke was elevated when women smoked or had a history of hypertension or diabetes. The presence of a risk factor for ischemic stroke in combination with oral contraceptive use increased the risk of stroke even more (except for diabetes), although the numbers in some subgroups were quite small.

Discussion

Results of the RATIO Study

The aim of the present study was to assess the ischemic stroke risk for currently used oral contraceptives. We confirmed the finding of others,^{16,17,26} ie, that the use of any type of oral contraceptives increases the risk of ischemic stroke, and we found a 2-fold increased stroke risk compared with no use. The results did not show a different effect between brands containing second- or third-generation progestogens. We also did not find a differential effect according to estrogen dose. The risk of oral contraceptives was even more elevated in combination with the presence of smoking, hypertension, hypercholesterolemia, or obesity. Because almost all of the patients were white, our findings probably should be limited to this ethnic group.

Comparison of the Results With Earlier Reports

The RATIO study is one of the largest studies showing the effect on ischemic stroke of progestogen type used in second- and third-generation oral contraceptives without the influence of estrogen dose. A few earlier reports^{16–19} estimated these risks as well. All of them found a 2-fold increased risk for second-generation oral contraceptives. However, the results for third-generation oral contraceptives were conflicting: Heinemann et al¹⁷ found an OR of 3.1 compared with 1.3, which was reported by Lidegaard and Kreiner,¹⁸ and 1.7, which was reported by the World Health Organization¹⁶ and Poulter et al.¹⁹ However, the number of patients in these last 2 studies was small; therefore, the statistical power was low.

We did not find an effect according to estrogen dose among oral contraceptives containing the same progestogen (ie, levonorgestrel). These results are difficult to compare with other studies because most of them ignore the pharmacological effects of the accompanying progestogen. However,

TABLE 5. Adjusted ORs (95% CI) for Ischemic Stroke in Relation to Ethinylestradiol Dose

| | Stroke Patients, n | Control Subjects, n | OR* (95% CI) |
|---|-----------------------|------------------------|---------------|
| 50 µg ethinylestradiol vs noncurrent use† | 3 | 10 | 2.3 (0.6–9.0) |
| 30 µg ethinylestradiol vs noncurrent use† | 28 | 94 | 2.4 (1.4–4.1) |
| 30 µg vs 50 µg ethinylestradiol | 28/3 | 94/10 | 0.7 (0.1–3.2) |

*Adjusted for stratification factors (age, area of residence, and calendar year).
 †Relative to nonusers: 101 patients and 568 control subjects. Analyses were restricted to OCs with 50 µg ethinylestradiol and 125 µg levonorgestrel and OCs with 30 µg ethinylestradiol and 150 µg levonorgestrel.

TABLE 6. ORs of Ischemic Stroke in Relation to Current OC Use According to Other Risk Factors for Stroke

| | Noncurrent OC Use | | Current OC Use | |
|----------------------|---------------------------|----------------|---------------------------|-----------------|
| | Patients/Control Women, n | OR* (95% CI) | Patients/Control Women, n | OR* (95% CI) |
| Smoking | | | | |
| No | 41/338 | 1 (Reference) | 36/183 | 2.8 (1.5–5.0) |
| Yes | 60/228 | 2.3 (1.5–3.6) | 66/165 | 4.4 (2.7–7.3) |
| Hypertension | | | | |
| No | 69/532 | 1 (Reference) | 86/327 | 2.7 (1.8–4.0) |
| Yes | 32/36 | 6.8 (3.7–12.2) | 16/19 | 7.6 (3.5–16.3) |
| Hypercholesterolemia | | | | |
| No | 96/547 | 1 (Reference) | 97/344 | 2.1 (1.5–3.1) |
| Yes | 5/20 | 1.1 (0.4–3.3) | 5/3 | 10.8 (2.3–49.9) |
| Diabetes | | | | |
| No | 92/556 | 1 (Reference) | 99/345 | 2.3 (1.6–3.4) |
| Yes | 9/11 | 5.6 (2.1–15.2) | 2/2 | 5.3 (0.7–42.6) |
| Obesity | | | | |
| No | 77/476 | 1 (Reference) | 77/300 | 2.2 (1.5–3.0) |
| Yes | 19/76 | 1.2 (0.7–2.2) | 22/37 | 4.6 (2.4–8.9) |

Total numbers may differ because of missing data.

*Relative to the reference group, adjusted for stratification factors (age, area of residence, and calendar year).

Lidegaard and Kreiner¹⁸ found an increased risk of stroke for users of high-estrogen oral contraceptives, and they failed to find a trend according to estrogen dose after adjustment for progestogen types.

We observed an increased risk of ischemic stroke for the use of any type of oral contraceptives. In patients aged 18 to 29 years, the OR was lower, but this probably should be attributed to the high prevalence of oral contraceptive use in this age group (81% among stroke patients versus 78% among control women). Our estimate is somewhat lower than the estimates in earlier studies^{16,17,26}; however, 2 other studies showed lower ORs.^{27,28}

Effect of Other Risk Factors for Ischemic Stroke

The presence of obesity or hypercholesterolemia in combination with oral contraceptive use increased the risk of stroke, although the oral contraceptive-associated OR for hypercholesterolemia was based on small numbers. The risk of stroke was also higher in users of oral contraceptives who had hypertension. This result is in agreement with the findings of the World Health Organization study,¹⁶ which determined that a history of hypertension is associated with a higher risk of stroke in oral contraceptive users and nonusers. In the Transnational study, Heinemann et al¹⁷ also found an increased risk in nonusers but did not find a risk difference for women using oral contraceptives, either with or without hypertension. Smoking was also a risk factor for stroke in oral contraceptive users. As already shown in other studies,^{16,17} risks associated with oral contraceptives were higher among current smokers compared with nonsmokers.

Aspects of the Design of the Study

The RATIO study is a multicenter case-control study in the Netherlands, where the percentage of oral contraceptive users

is fairly high. We calculated that a study that would have sufficient precision ($\alpha=0.05$, $\beta=0.20$) to demonstrate a 2-fold risk of stroke in users of third-generation oral contraceptives compared with users of second-generation pills would require 110 women with stroke and 220 control women, assuming that 50% of the controls would use a second-generation pill. Such a size would preclude definite conclusions about smaller risk differences; however, it would be sufficient to detect important differences. We did not power the study to address specifically the risk implications of first-generation pills; hence, we refrained from any concluding statements on this topic and merely reported our data, including the wide 95% CI (0.7 to 4.4) of its OR.

Because we used a frequently matched study design, we adjusted for the stratification factors (ie, age, area of residence, and index date). Additional adjustment for putative confounders did not affect the OR. This suggests that adjustment for the stratification factors removed virtually all confounding effects. Adjustments for multiple comparisons are not indicated because there were only a few primary comparisons of interest: (1) all contraceptives versus none and (2) third-generation versus second-generation contraceptives. The restriction of these comparisons to specific estrogen doses should not be regarded as separate comparisons.

In the present study, the prevalence of migraine was very low. This probably should be attributed to the relatively strict criteria: we asked whether a neurologist even confirmed this diagnosis or whether the woman used medication for migraine. We refrained from adjustments in our analyses for atrial fibrillation because we considered it to be a rare cause of stroke at young age. Moreover, it would have been questionable whether reliable data on this point could be obtained via a questionnaire from control women.

All observational studies are susceptible to bias. Associations between the use and type of oral contraceptives and the severity of stroke may have influenced our findings. Eighteen (6%) of the patients had died. Twenty-four (8%) patients refused participation, many of whom were impaired or felt too ill to participate. If pill use is related to stroke severity, this selection may have led to a slight underestimation of the true OR. Response bias among control women seems to be unlikely because the response rate was high (89%), and a strong relationship between oral contraceptive use and response rate among control subjects is not expected because the women were not informed about the primary objective of the present study.

Reliance on participation memory for information on oral contraceptive use and the presence of cardiovascular risk factors could have biased the results. In the present study, the presence of putative confounders were self-reported and not validated against medical records. For example, biased recall for a history of hypertension is a possibility among current oral contraceptive users because they are more likely to have had recent blood pressure checks. Reporting bias could have occurred because we found an imbalance between the educational status of the patient and control groups. However, our analyses did not indicate that education played an important role: the OR for any contraceptive use of 2.28 (95% CI 1.59 to 3.27, adjusted for the stratification factors) hardly changed after additional adjustment for education level (OR 2.17, 95% CI 1.50 to 3.14). Selective memory about oral contraceptive exposure could also have occurred in the patients as a result of the severity of ischemic stroke compared with the healthy control women. Therefore, we used color photographs of all oral contraceptive pills marketed in the Netherlands to help women recall specific brands or oral contraceptives used. It was not possible to validate the contraceptive history against medical records or prescriptions because the pharmacies destroyed these data after 5 years.

Incorrect diagnosis of stroke is unlikely to have played an important role. Only hospital-confirmed diagnoses of ischemic stroke were recorded, and particularly among young patients, diagnostic procedures are thorough. Transient ischemic attack was excluded from the stroke analyses because its diagnosis has only limited reliability.

Selective prescription of oral contraceptives depending on the characteristics of the patient or the pills could have influenced the results. We investigated the use of oral contraceptives by risk factor status in the control women by weighted age-standardized rates and found little indication of selective prescription: women who smoked used oral contraceptives as often as women who did not (41% versus 34%, respectively), and the same was true for hypertension (36% in those with hypertension versus 40% in those without hypertension) and hypercholesterolemia (37% in those with hypercholesterolemia versus 31% in those without hypercholesterolemia). Only in diabetic women were oral contraceptives less prescribed than in nondiabetic women (14% versus 37%, respectively), but the number of diabetic patients was small. The results of the analyses on the oral contraceptive–stroke relationship hardly changed when restricted to the women

with no risk factors for ischemic stroke, which also indicates that there was no confounding by indication.

Conclusions of the Study

Previous studies have strongly suggested that third-generation oral contraceptives are associated with a higher risk of venous thrombosis than second-generation oral contraceptives, particularly in young healthy women. Therefore, in these women, second-generation oral contraceptives are a better choice. The results of the present study show that progestogens used in third-generation oral contraceptives do not change the risk of ischemic stroke compared with progestogens used in second-generation oral contraceptives, even though they were developed to reduce the risk of arterial thrombosis. Furthermore, we confirm the findings of previous studies that current oral contraceptive use versus no use is associated with a higher risk of ischemic stroke, especially in older age groups. Separately, we report on the effects on myocardial infarction and peripheral artery disease. The present study, together with previous studies on venous thrombosis, will allow decision-based analyses and rational contraceptive prescription to individual women.

Appendix

The participating centers and those involved are as follows: University Hospital Maastricht, J. Boiten; University Hospital Rotterdam-Dijkzigt, P.J. Koudstaal; University Medical Centre, Amsterdam, J. Stam; Canisius Wilhelmina Hospital, Nijmegen, C.W.G.M. Frenken; Leiden University Medical Centre, E.L.E.M. Bollen; Rijnstate Hospital, Arnhem, Q.H. Leyten; Sint Antonius Hospital Nieuwegein, H.W. Mauser; University Medical Centre Utrecht, L.J. Kappelle; and Atrium Medical Centre Heerlen, C.L. Franke.

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