RISK OF ISCHEMIC STROKE ASSOCIATED WITH LOW-DOSE ORAL CONTRACEPTIVE USE: A META-ANALYSIS

Dae Hyun Kim, MD, MPH¹, Joachim Bleys, MD, MPH², Marlis Gonzalez-Fernandez, MD³,
Rebecca Gottesman, MD⁴ and Michelle Hudspeth, MD⁵

Abstract

Context: Oral contraceptive (OC) use has been shown to be associated with increased risk of ischemic stroke. However, most studies were conducted before low-dose OC became available.

Objective: To determine whether low-dose OC use is associated with increased risk of ischemic stroke

Data Sources: All relevant human-subject and English-language studies in MEDLINE, EMBASE, and Science Citation Index from January 1970 through February 2005

Study Selection and Data Extraction: All published studies of OC or estrogen with any type of stroke as an outcome were included. Studies were excluded if they included populations at high risk for ischemic stroke or did not include low-dose OC use, ischemic stroke, or a control group.

Data Synthesis: A meta-analysis of the nine included studies showed positive association between current low-dose OC use and ischemic stroke (Overall pooled odds ratio [OR], 2.1; 95% confidence interval [CI], 1.7 - 2.7). Compared to never users, current users had slightly higher risk (OR, 1.2; 95% CI, 0.4 - 3.2) and former users had significantly lower risk (OR, 0.6; 95% CI, 0.5 - 0.7). Current users of second and third generation OC had 2.4 times (95% CI, 2.0 - 3.0) and 2.0 times (95% CI, 1.3 - 3.0) increased risk of ischemic stroke, respectively, compared to former or never users. The independent effect of low-dose OC use on the risk of ischemic stroke was stronger among women less than 35 years, nonsmokers, and normotensive women.

Conclusion: Current use of low-dose OC compared to former or never use is associated with about two times increased risk of ischemic stroke. However, considering its health benefits and effectiveness of birth control and very low incidence of ischemic stroke in young women, use of low-dose OC is generally safe.

1. Department of Medicine, Thomas Jefferson University, Philadelphia, PA
2. Welch Center for Prevention, Epidemiology, and Clinical Research, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
3. Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD
4. Department of Neurology and Neurosurgery, Johns Hopkins University, Baltimore, MD
5. Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD

Background

Since the introduction of oral contraceptive (OC) in the late 1950s, a number of epidemiologic studies have shown that OC use is associated with increased risk of ischemic stroke.^{1,2} However, most of the studies conducted before 1980s were based on OCs containing high-dose estrogen (80 or 100 µg) that are no longer used. Oral contraceptives containing low-dose estrogen (less than 50 µg) became available in the early 1970s. The formulation currently in widespread use in the United States contains 30 or 35 µg of estrogen.³ Thus, it is not reasonable to generalize about the risk of ischemic stroke associated to the use of low-dose OC from the findings based on high-dose formulations.

There are not many studies that examined the risk of ischemic stroke among low-dose OC users. Although it seems that reduction in estrogen content decreases the thrombogenicity of OCs and lowers the risk of ischemic stroke, there is a heterogeneity in the reported risk among studies.^{4,6} Some studies reported small increase,^{5,8} whereas others reported no increase in the risk of ischemic stroke.^{9,10} Considering the lack of feasibility of conducting randomized controlled trials and only limited number of observational studies showing inconsistent results, it is important to summarize the findings from observation studies and investigate possible reasons for this inconsistency. This will provide useful information on potential health risk of OCs that are currently used by over 76 million women worldwide.¹¹

Here, we conducted a meta-analysis to evaluate existing evidences to determine whether low-dose OC use is associated with increased risk of ischemic stroke and to quantify this risk among subgroups with different characteristics. Specifically, we included only premenopausal women who comprise the majority of OC users. The exposure was confined to the use of OCs containing less than 50 µg of estrogen that are currently in widespread use. The outcome was limited to ischemic stroke, because the strength of association between OC use and hemorrhagic stroke is not strong.¹² We reviewed all relevant cohort studies and case-control studies that were conducted in the United States as well as internationally.

Methods

Study Selection

We conducted a literature search using MEDLINE, EMBASE, and Science Citation Index (January 1970 through February 2005). The following key words and subject terms were used: (intracerebral hemorrhage OR venous sinus thrombosis OR cerebral infarct OR cerebral ischemia OR cerebrovascular accident OR cerebrovascular disease OR stroke) AND (oral contraceptive OR birth control pill OR estrogen). The search was restricted to English and humans. The original search yielded 1183 citations from MEDLINE, 730 from Science Citation Index, and 132 from EMBASE (excluding duplicates from MEDLINE), for a total of 2045 citations.

Figure 1. Retrieval of Eligible Studies

A preliminary title review was done by five investigators and 377 potentially eligible articles were selected for abstract review. Each abstract was reviewed independently by two investigators, with the following exclusion criteria:

1. hormone replacement therapy,
2. inclusion of postmenopausal women without stratification,
3. subarachnoid or subdural hemorrhage as the only primary outcome,
4. estrogen dose exclusively more than 50 mg (first generation OCs) or dose not specified or progesterone-only contraceptives,
5. stroke not as a primary outcome,
6. women with coagulation disorders,
7. case series without controls, and
8. recurrent stroke.

With these exclusion criteria, we excluded 277 articles. Considering the time when high-dose OCs were withdrawn from the market and low-dose OCs became widely available, we further

restricted our analysis to the articles published since 1985, which left 55 articles for full-text review. The 55 articles identified during the literature search were reviewed by an investigator (who initially had not reviewed the abstract of the article in question) who reassessed the article and discussed the reasons for inclusion or exclusion with the rest of the investigators. From the 55 articles, we excluded 6 studies because of the inclusion of postmenopausal women without stratification, 4 because of fatal stroke or hemorrhagic stroke as the only outcome, 5 because of duplicate publications using the same data, and 10 because of the lack of comparison group (case series only). Ten articles were excluded, because they were published as abstracts only, review articles, letters to editor, or editorials and did not contain enough information for the analysis. We also exclude 11 studies that were conducted before 1990 and did not specify estrogen dose. Finally, data from nine remaining studies were abstracted for our analysis (See Figure 1). There were no randomized controlled trials or cohort studies that satisfied our criteria.

Data Abstraction

Data were abstracted by the reviewers of each study and verified by the rest of the investigators. Any disagreements were resolved through full discussion. Information on study quality as well as data was collected. Years of study conducted, study region, type of control (hospital or population control), age distribution of participants, and numbers of case and control were abstracted. Outpatient control was considered as hospital control. Definition of current OC users varied among studies and we followed the definition used by individual studies. Non-current users were defined as both former and never users. Estrogen dose was defined as low-dose, either when an OC contained less than 50 μ g of estrogen or when it belonged to second or third generation. The generation of OCs was determined by estrogen dose and types of progesterone⁷. Although the definition of generation was not consistent among studies, estrogen dose in each generation was consistent among studies (50 μ g or more for first generation, 30–40 μ g for second generation, and 20–30 μ g for third generation) and we followed the classification used by each study. Estrogen dose or generation of OCs was abstracted from each study when it was mentioned in the article. When it was not mentioned, it was estimated from the prevailing use pattern in the study area during the study period. Generally, the estrogen dose was assumed to be less than 50 μ g if a study was conducted after 1990. When a study was conducted before 1990 and did not specify the estrogen dose or generation of OCs, it was excluded from our analysis. Information on exposure to OCs (current, past, or never use) was obtained. Information on definition of stroke and diagnostic methods, such as use of clinical or radiographic diagnosis or both, was gathered. We excluded hemorrhagic stroke, such as subarachnoid, intracranial, and intraparenchymal hemorrhage. Refusal rate was calculated separately for cases and controls as the percentage of eligible individuals who declined to participate in a study.

Table 1. Characteristics of Nine Eligible Case-Control Studies for Data Abstraction

Source (Year)	Region	Years of Study	Control Type	Age (Years)	Case/Control#	Estrogen Dose (g)	Exposure Assessment	Stroke Type	Stroke Diagnosis	Case/Control Refusal Rate (%)
Lidegaard et al. (1993)	Denmark	1985-1989	P	15 - 44	320 / 1197	≥50, 30-40, 20	Questionnaire	Ischemic	Clinical	2.2% / 0.1%
Petitti et al. (1996)	US	1991-1994	P	15 - 44	295 / 774	<50	Interview	Ischemic Hemorrhagic	Clinical	9.6% / N
WHO Collaborative (1996)	International	1989-1993	H	15 - 49	697 / 1952	≥50, <50	Interview	Ischemic	Clinical	13.7% / NS
Barinagarrementeria et al. (1998)	Mexico	1987-1998	H	11 - 40	130 / 122	NS	NS	Ischemic	Clinical Radiologic	NS / NS
Heinemann et al. (1998)	Europe	1993-1996	P, H	16 - 45	220 / 775	≥50, <50	Interview	Ischemic	Clinical Radiologic	NS / NS
Chang et al. (1999)	Europe	1990-1994	H	20 - 44	291 / 736	≥50, <50	Interview	Ischemic	Hemorrhagic Clinical	NS / NS
Kemmeren et al. (2002)	Netherlands	1990-1995	P	19 - 49	203 / 916	≥50, <50	Questionnaire	Ischemic	Clinical Radiologic	31% / 27%
Lidegaard et al. (2002)	Denmark	1994-1998	P	15 - 44	609 / 3946	≥50, 30-40, 20	Questionnaire	Ischemic	Clinical	2.2% / 0.5%
Nightingale et al.* (2004)	UK	1992-1998	P	15 - 49	187 / 1129	NS	UK GPRD	Ischemic	Clinical Radiologic	NS / NS

Abbreviations: WHO, World Health Organization; P, population controls; H, hospital controls; NS, not specified; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index; RHD, rheumatic heart disease; FH, family history; OC, oral contraceptive; UK GPRD, UK General Practice Research Database

* Nested case-control study using the UK General Practice Research Database`

Risk estimates used in our meta-analysis were determined a priori. For the primary analysis, the odds ratio (OR) comparing current with non-current users after adjusting for potential confounders was chosen and pooled. Standard errors were calculated from adjusted odds ratios and their 95% confidence intervals (CIs). Information about potential confounders that were adjusted for in individual studies was also collected. When a study did not provide the adjusted odds ratio or its 95% CI comparing current with non-current users, we excluded the study from the analysis⁴. In subgroup analyses, we dichotomized age as 35 years or more vs. less than 35 years, smoking as current vs. non-current smokers, and hypertension as present vs. absent. Then we collected the data relevant to ischemic stroke from each stratified analysis.

Statistical Analysis

We combined the odds ratios (ORs) comparing current with non-current users from each study using both fixed-effects model and DerSimonian and Laird random-effects model¹³. However, results from the random-effects model are presented in this report because significant heterogeneity was identified among studies. In the four studies⁵⁻⁸ that provided adjusted ORs for each generation of OCs, we combined the adjusted ORs for second and third generations using the random effects model. In a study¹⁴ that had stratification

by presence or absence of migraine, overall adjusted OR was calculated in a similar fashion. A forest plot was created using adjusted ORs and 95% CIs from each study. One study⁴ that did not provide the adjusted OR of ischemic stroke comparing current with non-current users was not included when calculating overall OR, but included in other analyses. Heterogeneity among studies was calculated using chi-square test and studies were defined as heterogeneous when p-value was less than 0.05.

Preplanned subgroup analyses were performed according to exposure classification (current vs. never users and former vs. never users), progesterone type (second generation, third generation, and second vs. third generation), and presence or absence of other risk factors for ischemic stroke (≥ 35 years old vs. < 35 years old, smokers vs. non-smokers, and hypertensives vs. normotensives). To evaluate which study characteristics contributed to the heterogeneity, we examined the influence of study characteristics on overall OR by applying different inclusion criteria. In addition, the influence of each study was evaluated by eliminating each study at a time and calculating the resultant overall OR after the study was excluded. To examine the presence of publication bias, Egger's test and Begg's test were performed and a funnel plot was plotted. All statistical analyses were performed using STATA 8.2.

Results

Qualitative Analysis

The characteristics of nine case-control studies that satisfied our criteria were summarized (Table 1). Among the selected studies, six^{4, 6-8,14,15} were conducted in Europe, one⁹ in the US, one¹⁶ in Mexico, and one⁵ in Europe and developing countries in Asia, Africa, and Latin America. Three studies^{5,7,14} involved participants from more than one country. All the studies were conducted since 1985 and published since 1993. Five studies^{4,6,8,9,15} used population control, three^{5,14,16} used hospital control, and one⁷ used both. Age distribution of study subjects ranged from 11 to 49 years old. The number of cases varied from 130 in the study by Barinagarrementeria et al¹⁶ to 697 in the study by World Health Organization (WHO) collaborative.⁵ There was only one study⁹ in which estrogen dose in OCs was exclusively less than 50 µg. Six studies^{4,8,14} reported both estrogen dose less than 50 µg and greater than 50 µg. Two studies^{15,16} did not state estrogen dose explicitly. As for the study outcome, seven studies^{4,8,15,16} reported ischemic stroke and two studies^{9,14} reported both ischemic and hemorrhagic stroke.

Several methodological issues were examined. In most studies, exposure to OCs was measured by mailing questionnaires^{4,6,8} or personal interviews.^{5,7,9,14} One study¹⁶ did not report how they obtained the information on OC exposure and one study¹⁵ used General Practice Research Database which is an automated national database collected for research purpose and contains medical and prescribing records for more than 8.5 million people throughout the UK. With regard to outcome ascertainment, four studies^{7,8,15,16} used a combination of clinical and radiological diagnosis, whereas five studies^{4,6,9,14} used only clinical diagnosis.

Cases and controls were matched for age in eight studies.^{4-7,9,14-16} Age was adjusted in three studies⁶⁻⁸ and socioeconomic status was adjusted in two studies.^{6,14} Smoking was adjusted in eight studies^{4-9,14,15} and hypertension was adjusted in seven studies.^{5,7-9,14,15} Four studies^{7-9,15} adjusted for diabetes. The study by Lidegaard et al⁶ controlled for hypertension and diabetes in their initial model, but excluded them from the final model because of lack of confounding influence by the variables. The study by Barinagarrementeria et al¹⁶ did not provide any information on potential confounders that they adjusted for (Figure 2).

All of the studies except for one study⁴ reported adjusted OR comparing current with non-current users. Adjusted OR comparing current with never users was provided in two studies^{4,9} and adjusted OR comparing ever vs. never users was provided in one study.⁹ There were three studies⁷⁻⁹ reporting OR by smoking, two studies^{8,9} reporting OR by age, four studies⁵⁻⁸ reporting OR by the generation of OCs, three studies⁷⁻⁹ reporting OR by history of hypertension, and one study¹⁴ reporting OR by history of migraine.

The definition of exposure to OCs was inconsistent among studies. Current OC use was defined as the use of OCs within 1 month up to 1 year.

Quantitative Analysis

The overall pooled OR for ischemic stroke comparing current with non-current users calculated by the random-effects model was 2.14 (95% CI, 1.69 - 2.72) (Figure 2). Significant heterogeneity was observed among studies ($P = 0.02$).

In the subgroup analysis by exposure classification, there was weak evidence that current users were associated with increased risk of ischemic stroke compared to never users (OR, 1.18; 95% CI, 0.44 - 3.16) (See Table 2). In contrast, former users were associated with decreased risk compared to never users (OR, 0.58; 95% CI, 0.48 - 0.71). By progesterone type, second generation was associated with 2.41 times increased risk of ischemic stroke (OR, 2.41; 95% CI, 1.96 - 2.96) and third generation was associated with 1.98 times increased risk (OR, 1.98; 95% CI, 1.29 - 3.03). Third generation OCs seemed to be associated with less increase in risk compared to second generation, but there was little difference between the two formulations in direct comparison. Test of heterogeneity was not significant among studies pooled for current vs. never users and for third generation OCs.

Current use of low-dose OCs was associated with 1.2 times increase in risk of ischemic stroke among women of 35 years or older (OR, 1.20; 95% CI, 0.19 - 7.56) and 1.48 times increase among women less than 35 years (OR, 1.48; 95% CI, 0.77 - 2.83). Non-smokers who currently use OCs (OR, 2.60; 95% CI, 1.49 - 4.54) seemed to have higher risk of ischemic stroke than smokers (OR, 2.09; 95% CI, 1.68 - 2.59). Similarly, increase in risk of ischemic stroke related to OC use was greater among normotensive women (OR, 2.55; 95% CI, 1.50 - 4.32) than among hypertensive women (OR, 0.71; 95% CI, 0.22 - 2.31).

The findings from the analysis examining the influence of study characteristics on overall pooled OR were presented (Table 3). When we included four studies that used radiographic imaging for the diagnosis of stroke, the pooled OR changed from 2.14 to 2.45. The combined OR was 2.81 when the studies with population control were all excluded, whereas it was 1.89 when the studies with hospital control were all excluded. Significant heterogeneity was observed only when the studies that did not report estrogen dose were excluded.

Sensitivity Analysis

The influence of each study on overall OR was examined (Figure 3). The study published in 2002 by Lidegaard et al⁶ had moderate influence on overall OR. Overall OR after omitting the study by Lidegaard et al⁶ was 2.42 (95% CI, 1.98 - 2.94). Omission of other studies made little difference.

Publication Bias

The possibility of publication bias was evaluated by using the Egger's test (weighted regression) and Begg's test (rank correlation method). P-value for bias in the Egger's test was 0.62 and p-value in Begg's test was 0.75. A funnel plot showed symmetry around the overall pooled OR, indicating the absence of publication bias (Figure 4).

Figure 2. Overall Odds Ratio Comparing Current vs. Non-current Users for Ischemic Stroke and 95% Confidence Intervals (CIs)*

Abbreviations: WHO, World Health Organization; SES, social economic status; Smk, smoking; HTN, hypertension; DM, diabetes mellitus, NS, non specified

* Lidegaard et al. (1993) was not included in calculating overall odds ratio, because it did not provide the odds ratio comparing current vs. non-current users. Two components of WHO collaborative (1996) - Europe vs. Developing countries (Asia, Africa, and Latin America) were considered separately.

Table 2. Pooled Odds Ratios and 95% Confidence Intervals (CIs) of Ischemic Stroke from Stratified Meta-analyses*

Data Stratifications	Number of Studies Pooled (References)†	Pooled Odds Ratio (95% CI)	Test for Heterogeneity P-value
All studies	9 (4, 5, 6, 7, 8, 9, 14, 15, 16)	2.14 (1.69 - 2.72)	0.02
Exposure classification			
Current vs. Never users	2 (4, 9)	1.18 (0.44 - 3.16)	0.06
Former vs. Never users	2 (4, 9)	0.58 (0.48 - 0.71)	0.55
Progesterone type			
2nd generation	5 (5, 6, 7, 8)	2.41 (1.96 - 2.96)	0.33
3rd generation	5 (5, 6, 7, 8)	1.98 (1.29 - 3.03)	0.07
3rd vs. 2nd generation	2 (7, 8)	1.12 (0.76 - 1.64)	0.63
Independent effect of oral contraceptive use among:			
≥ 35 years old	2 (8, 9)	1.20 (0.19 - 7.56)	0.06
< 35 years old	2 (8, 9)	1.48 (0.77 - 2.83)	0.71
Smokers	3 (7, 8, 9)	2.09 (1.68 - 2.59)	0.33
Non-smokers	3 (7, 8, 9)	2.60 (1.49 - 4.54)	0.14
HTN present	2 (7, 8)	0.71 (0.22 - 2.31)	0.06
HTN absent	3 (7, 8, 9)	2.55 (1.50 - 4.32)	0.08

Abbreviation: HTN, hypertension

* Pooled odds ratios are comparing current vs. non-current oral contraceptive users, except for those under exposure classification.

† The study by WHO collaborative⁵ was counted as two separate studies (Europe and developing countries).

Discussion

In our meta-analysis, all the nine studies showed positive association between current low-dose OC use and ischemic stroke and six of them had statistically significant association. The overall pooled OR of ischemic stroke among current low-dose OC users, compared with non-current users, was 2.14 (95% CI, 1.69 - 2.72) (Figure 2). Therefore, our meta-analysis suggests that low-dose OC use is a risk factor for ischemic stroke.

Among the nine included studies, the study published in 1993 by Lidegaard et al¹⁴ was not included when calculating overall OR, because the authors did not report the standard error or 95% CI associated with the adjusted OR of 3.46 comparing current with non-current users. The study by WHO collaborative⁵ had two distinct components - Europe and developing countries including Asia, Africa, and Latin America - showing different results and it was considered as two different studies. The studies by Barinagarrementeria¹⁶ and Nightingale¹⁵ were included despite the lack of information on estrogen dose, because the dose was estimated to be less than 50 µg considering the region and years of study. During the literature search, we found three cohort studies,¹⁷⁻¹⁹ but they did not meet our criteria. One cohort study by Stampfer et al¹⁷ was conducted from 1976 through 1984 and did not have information on estrogen dose. Considering the time period when it was conducted, we suspected that it had included a significant proportion of high-dose OC users. The other two cohort studies that were conducted from 1980 through 1982 by Porter et al¹⁸ and from 1968 through 1994 by Mant et al¹⁹ reported only proportion of low-dose OC users without stratified results. High-dose OC users consisted of 59% in the study by Porter et al¹⁸ and over 32% in the study by Mant et al.¹⁹ We were unable to extract the data related to low-dose OC use from the three cohort studies. They were not included in the analysis, because including significant proportion of high-dose OC users will overestimate the risk of ischemic stroke.

Significant heterogeneity was observed when we combined all the studies to obtain the overall pooled OR ($P = 0.02$). It is because all the included studies are case-control studies of varying qualities and characteristics. They are particularly susceptible to confounding and bias, compared to cohort studies and randomized controlled trials.²⁰ Each study recruited participants at variable risk by applying different inclusion and exclusion criteria and used different methods for assessing exposure and ascertaining outcome. Thus, we used the DerSimonian and Laird random-effects model to encompass non-random variation between study results and allow more conservative CI for the overall OR.¹³ Residual confounding always exists in a meta-analysis of observational studies. Some studies did not measure or control for important risk factors for ischemic stroke, such as age, smoking, hypertension, and diabetes (Figure 2). In addition, there are several potential sources for bias in case-control studies. Information on past

exposure to OCs relies on participants' recall and the extent of recall between cases and controls tends to be different, leading to biased results. The studies by Lidegaard et al^{4, 6} and Kemmeren et al⁸ mailed questionnaires to participants, whereas the studies by Petitti et al⁹, WHO collaborative⁵, Heinemann et al⁷, and Chang et al¹⁴ used personal interviews based on standardized questionnaires. The accuracy of information collected by these methods varies among studies and is a source of information bias. Only Nightingale et al¹⁵ used a reliable database that has medical and prescribing records collected for research purpose. Classification of exposure to OCs was also inconsistent between studies. Differential refusal to participate in the study between cases and controls may indicate the presence of selection bias.

We performed subgroup analyses to examine how the association between low-dose OC use and risk of ischemic stroke changes according to exposure classification, progesterone types, and women with different risk factors for ischemic stroke (Table 2). Compared to never users, current users seemed to have slightly higher risk (OR, 1.18; 95% CI, 0.44 - 3.16) and former users had significantly lower risk (OR, 0.58; 95% CI, 0.48 - 0.71). Decreased risk in former users was consistent between studies. Possible explanation is that never users may have multiple risk factors and are at higher risk for ischemic stroke than users. Women who stopped taking OCs may be more health-conscious and have a reduced risk due to healthier lifestyle. Past use does not seem to have a long term "hangover" effect. Different progesterone formulation in OCs was also associated with different risk of ischemic stroke. This may be due to the effect of different progesterone components, different risk profiles between users of second generation and users of third generation, or preference of prescribing physicians between studies in different countries. Thus, it is possible to underestimate or overestimate the risk of ischemic stroke associated with third generation OC use. The independent effect of low-dose OC use on the risk of ischemic stroke was stronger among women less than 35 years compared to women of 35 years or older, nonsmokers compared to smokers, and normotensive women compared to hypertensive women. These results are not consistent with recent meta-analyses by Gillum et al²¹ and Chan et al¹² and some studies^{7, 19, 22} that suggested greater risk among OC users with additional risk factors for ischemic stroke. Because only small number of the selected studies reported stratified information on risk factors, the pooled estimates from our subgroup analyses are less precise, which may explain the inconsistency with previous reports.

To find out which study characteristics contributed to the heterogeneity, we examined the influence of certain study characteristics on the pooled OR (Table 3). When we only included the studies that used combination of clinical and radiological diagnosis, the overall OR was 2.45 (95% CI, 1.99 - 3.06) and test of heterogeneity was insignificant. Exclusion of two studies

Figure 3. Influence of Each Study on Overall Odds Ratio

that did not report estrogen dose made very little change in the overall OR and heterogeneity. Studies with population control had much lower pooled OR than studies with hospital control, meaning that control subjects from hospital underreported or less frequently used OCs for some reasons. We also evaluated the influence of each study on the overall OR by eliminating each study at a time (Figure 3). Although the study by Lidegaard et al⁶ appeared to have moderate influence, there was not one particular study that has significant influence on the overall OR.

A meta-analysis by Gillum et al²¹ on this topic reported in subgroup analyses that low-dose OC use is associated with about two times increased risk of ischemic stroke (Relative risk, 2.04; 95% CI, 1.51 - 2.76). Another recently published meta-analysis by Chan et al¹² also reported 2.7 times increase in risk for thrombotic stroke associated with low-dose OC use (OR, 2.74; 95% CI, 2.24 - 3.35). However, Chan et al¹² included the studies that did not have information on estrogen dose and their primary outcome was not confined to ischemic stroke. Our finding of 2.1 times increase (OR, 2.14; 95% CI, 1.69 - 2.72) is consistent with their findings.

This meta-analysis has several limitations. As mentioned above, a meta-analysis of observational studies has methodological limitations and susceptibility to bias and confounding, leading to

imprecise estimate of true association. We limited our analysis to the studies in which the exposure and outcome were clearly stated as low-dose OC and ischemic stroke, respectively. Therefore, only nine studies were included. This small number substantially limited our subgroup analyses and yielded less precise 95% CIs. Due to the small number, we could not conduct a meta-regression to assess risk of ischemic stroke related to low-dose OC use controlling for several study-level covariates. In addition, we could not investigate the dose-response relationship between low-dose OC use and ischemic stroke, because most of studies did not report the duration of OC use. As a result, potential biases and confounders were not adequately addressed and reasons for heterogeneity between studies were not sufficiently examined.

Presently, more than 10 million women in the United States and more than 76 million worldwide use OCs.¹¹ Our meta-analysis found that current use of low-dose OC increases the risk of ischemic stroke approximately by two times. However, when we consider its health benefits and effectiveness of birth control and very low baseline incidence of ischemic stroke in young women of less than 10 per 100,000²³, low-dose OC use in premenopausal women is generally acceptable and safe. Future research is warranted to identify high-risk groups for ischemic stroke associated with low-dose OC use and to investigate the dose-response relationship between the exposure and outcome. ■

Table 3. Influence of Study Characteristics on Overall Odds Ratios and 95% Confidence Intervals (CIs) of Ischemic Stroke*

Data Stratifications	Number of Studies Pooled (References)†	Pooled Odds Ratio (95% CI)	Test for Heterogeneity P-value
All studies	9 (5, 6, 7, 8, 9, 14, 15, 16)	2.14 (1.69 - 2.72)	0.02
Studies that used radiologic imaging for diagnosis of stroke	4 (7, 8, 15, 16)	2.45 (1.99 - 3.06)	0.78
Studies that reported estrogen dose	7 (5, 6, 7, 8, 9, 14)	2.10 (1.59 - 2.78)	0.01
Studies that used			
Hospital control	5 (5, 7, 14, 16)	2.81 (1.83 - 4.30)	0.22
Population control	5 (6, 7, 8, 9, 15)	1.89 (1.52 - 2.35)	0.20

* Pooled odds ratios are comparing current vs. non-current oral contraceptive users, except for those under exposure classification.

† The study by WHO collaborative⁵ was counted as two separate studies (Europe and developing countries).

References

- Masi AT, Dugdale M. Cerebrovascular diseases associated with the use of oral contraceptives. A review of the English-language literature. *Ann Intern Med.* Jan 1970;72(1):111-121.
- Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. *Br Med J.* Apr 27 1968;2(599):199-205.
- Speroff L, DeCherney A. Evaluation of a new generation of oral contraceptives. The Advisory Board for the New Progestins. *Obstet Gynecol.* Jun 1993;81(6):1034-1047.
- Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *Bmj.* Apr 10 1993;306(6883):956-963.
- Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet.* Aug 24 1996;348(9026):498-505.
- Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception.* Mar 2002;65(3):197-205.
- Heinemann LA, Lewis MA, Spitzer WO, Thorogood M, Guggenmoos-Holzmann I, Bruppacher R. Thromboembolic stroke in young women. A European case-control study on oral contraceptives. Transnational Research Group on Oral Contraceptives and the Health of Young Women. *Contraception.* Jan 1998;57(1):29-37.
- Kemmeren JM, Tanis BC, van den Bosch MA, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke.* May 2002;33(5):1202-1208.
- Petitti DB, Sidney S, Bernstein A, Wolf S, Quesenberry C, Ziel HK. Stroke in users of low-dose oral contraceptives. *N Engl J Med.* Jul 4 1996;335(1):8-15.
- Schwartz SM, Petitti DB, Siscovick DS, et al. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. *Stroke.* Nov 1998;29(11):2277-2284.
- United Nations. World Contraceptive Use 2003. New York: United Nations; 2003.
- Chan WS, Ray J, Wai EK, et al. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med.* Apr 12 2004;164(7):741-747.
- Egger M, SG, Altman DG. Systematic Reviews in Health Care; Meta-analysis in context. Second edition ed: BMJ Books; 2001.
- Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Bmj.* Jan 2 1999;318(7175):13-18.
- Nightingale AL, Farmer RD. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke.* Jul 2004;35(7):1574-1578.
- Barinagarrementeria F, Gonzalez-Duarte A, Miranda L, Cantu C. Cerebral infarction in young women: analysis of 130 cases. *Eur Neurol.* Nov 1998;40(4):228-233.
- Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH. A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. *N Engl J Med.* Nov 17 1988;319(20):1313-1317.
- Porter JB, Hunter JR, Jick H, Stergachis A. Oral contraceptives and nonfatal vascular disease. *Obstet Gynecol.* Jul 1985;66(1):1-4.
- Mant J, Painter R, Vessey M. Risk of myocardial infarction, angina and stroke in users of oral contraceptives: an updated analysis of a cohort study. *Br J Obstet Gynaecol.* Aug 1998;105(8):890-896.
- Rothman KJ GS. Modern Epidemiology. Second ed: Lippincott Williams & Wilkins; 1998.
- Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: A meta-analysis. *Jama.* Jul 5 2000;284(1):72-78.
- Oral contraceptives and stroke in young women. Associated risk factors. *Jama.* Feb 17 1975;231(7):718-722.
- Petitti DB, Sidney S, Quesenberry CP, Jr, Bernstein A. Incidence of stroke and myocardial infarction in women of reproductive age. *Stroke.* Feb 1997;28(2):280-283.