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Current use of oral contraceptives and the risk of first-ever ischemic stroke: A meta-analysis of observational studies

Zhenlin Xu [a], Ying Li [a,*], Shaowen Tang [a], Xiaoping Huang [a], Tong Chen [b]

[a] Department of Epidemiology & Biostatistics, School of Public Health, Nanjing Medical University, Nanjing, China
[b] Ningbo Municipal Center for Disease Control and Prevention, Ningbo, China

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ABSTRACT

Objective: To evaluate the risk of first-ever ischemic stroke associated with current use of oral contraceptive pills (OCPs), and to describe how the risk was influenced by estrogen dose, progestin type, and study characteristics.
Methods: We obtained relevant articles published between 1970 and March 2014 by conducting a search of Pubmed, Embase and the Cochrane Library. Two investigators independently identified eligible studies based on selection criteria in a two-step method. The quality of studies was assessed with the Newcastle-Ottawa scale. Pooled odds ratios were calculated with a random-effects meta-analysis model.
Results: A total of 18 independent studies (3 cohort studies and 15 case-control studies) were identified. The overall summary odds ratio for first-ever ischemic stroke risk associated with current OCP use compared with noncurrent OCP use was 2.47 [95% confidence interval (CI), 2.04-2.99]. The risk of ischemic stroke among current OCP users decreased significantly with decreasing estrogen dose: OCPs of ≥ 50 μg ethinyl estradiol (EE), 30-40 ug EE, 20 ug EE and progestin only pills implied odds ratios of 3.28 (95%CI, 2.49-4.32), 1.75 (95%CI, 1.61-1.89), 1.56 (95%CI, 1.36-1.79), and 0.99 (95%CI, 0.71-1.37), respectively. All four generations of progestin were associated with an elevated risk of ischemic stroke, and the risk of ischemic stroke among users of the fourth-generation progestins seemed to be slightly lower than those of other generations of progestins.
Conclusions: Data from observational studies suggest that current use of modern OCPs is associated with an increased risk of first-ever ischemic stroke. OCPs containing lower estrogen doses incline to contribute to a smaller elevated risk of ischemic stroke.

Introduction

Oral contraceptive pills are the most common method of birth control used in the United States, with more than 10 million women relying on it [1]. Since the introduction of OCPs in the 1960s, several cardiovascular diseases [2], including stroke, venous thromboembolism, myocardial infarction, and pulmonary embolism, have been reported be associated with OCP use.

Ischemic stroke is an uncommon disease among healthy women of childbearing age with an annual incidence increasing with age [3]. The association between OCP use and ischemic stroke risk has been assessed in many studies. The results had been summarized in a meta-analysis [4] published in 2000, which found the risk of ischemic stroke in women exposed to OCP was significantly increased. However, this meta-analysis included several early studies [2,5] performed in the 1960s, which were with the absence of radiologic imaging to confirm the diagnosis of ischemic stroke. These early studies could bring a strong potential bias to the summary results. And since the meta-analysis, two large cohort studies [6,7] and five case-control studies [3,8–11] have been published, increasing the available sample from just over 25 000 to more than 1 700 000. These new studies still provided conflicting results regarding to the effects of OCPs on the risk of ischemic stroke. Furthermore, the formulations of OCPs have dramatically changed in recent years. The estrogen dose has decreased from an initial dose of 150 ug to present doses of 20-35 ug [12]. Some new progestions have been introduced to markets, such as drospirenone, which have theoretical advantages to progestin that have less androgenicity [13]. These new formulations of OCPs seemed to produce a modified risk of ischemic stroke [7–9].

In this article, we evaluated the current evidence on the association between the current use of OCPs and first-ever ischemic stroke by systematically reviewing the literature and conducting a meta-analysis. We also investigated potential modifying factors of the association between current OCP use and ischemic stroke, including estrogen dose, progestin type, several risk factors and study characteristics.

Methods

We followed the guidelines published by the MOOSE group [14] for designing, performing and reporting this meta-analysis.

* Corresponding author. Tel.: +86 2586576000; fax: +86 2586557840.
E-mail address: liying2008@qq.com (Y. Li).

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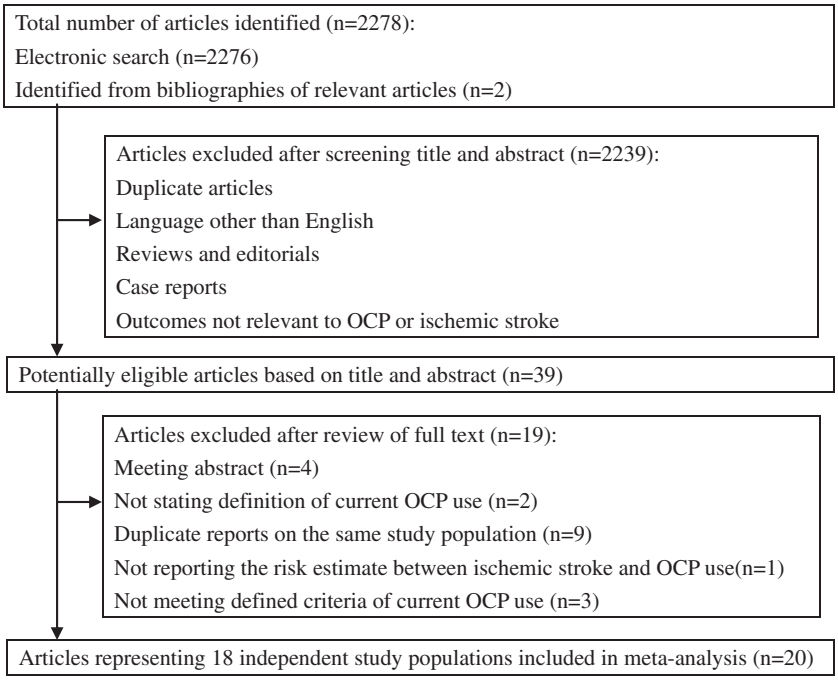

Fig. 1. Process of study selection.

Study Selection

Two investigators (ZL Xu and XP Huang) independently conducted searches of Pubmed, Embase and the Cochrane Library from 1970 to March 2014 using the following key words and subject terms "cerebral infarction" or "thrombotic stroke" or "ischemic stroke" or "cerebral ischemia" or "stroke" in combination with "oral contraceptive" or "birth control pill". Besides, we manually searched bibliographies of all pertinent primary articles and reviews for additional references.

A two-step selection process was used to identify eligible studies. Firstly, two investigators independently screened the title and abstracts of all potential primary articles and identified those studies meeting any inclusion criteria. Subsequently, those relevant articles selected or those without available abstracts were reviewed by evaluating their full text versions. If multiple studies were published from the same study population, only the study with the report of the longest follow-up or the larger number of participants was included. At each step, disagreements were adjudicated by a third investigator (T Chen).

Studies were included in the meta-analysis if: 1) they had a clear statement of diagnostic criteria for first-ever ischemic stroke; 2) they were controlled study (randomized controlled trial, cohort study or case-control study); 3) odds ratios or relative risks and 95% confidence intervals comparing OC current users to nonusers were provided or sufficient data were provided to allow us to calculate these numbers; 4) potential confounders were controlled for in the study design or analysis; 5) they were published in English language and in peer-reviewed journals.

Data Extraction

Two investigators (ZL Xu and XP Huang) independently extracted data from included articles. Disagreements were resolved by consensus. Risk estimates abstracted were those controlled for the greatest number of potential confounders by stratification, matching or multivariate analysis. Current use of oral contraceptives was defined as use ranging from at the time of the ischemic stroke event to within 12 months. Noncurrent use of OCPs was defined as either past or never use of OCPs.

Ischemic stroke was defined as occlusion and stenosis of cerebral and precerebral arteries on the basis of International Classification of Diseases-10. First-ever ischemic stroke was defined as the new onset of rapidly developing symptoms and signs of ischemic cerebral lesion that lasted at least 24 hours. A well-defined diagnosis of ischemic stroke was defined as one verified by computed tomography, magnetic resonance imaging, or cerebral angiography. The information of estrogen dose and progestin generation were abstracted if they were available. According to estrogen dose, oral contraceptive pill formulations were divided into five categories: 20 ug EE, 30-40 ug EE, $<$50 ug EE (including 20 ug EE and 30-40 ug EE), $\geq$50 μg EE and progestin only pills (POP). OCP formulations were classified on the basis of progestin type: first-generation progestins included norethindrone, lynestrenol, ethynodiol diacetate; second-generation included levonorgestrel, norgestrel; third-generation included gestodene, desogestrel, norgestimate; fourth-generation included: drospirenone, dienogest, cyproterone acetate [15]. Smoking status, alcohol use, body mass index, and history of hypertension, diabetes, migraine, and lipid abnormality were directly abstracted from included studies.

All data were directly taken from the included studies and we did not consult the authors for further information.

Quality Assessment

We evaluated the methodological quality of the included studies by using the Newcastle-Ottawa scale (NOS) [16]. This scale assesses the study's overall risk of bias in three domains: selection of study group, comparability of groups, and ascertainment of exposure and outcomes. The assessment score for an observational study ranged from 0 to 9. Two researchers (ZL Xu and XP Huang) independently assessed quality, and discrepancies were resolved by consensus.

Statistical Analysis

The measures of risk estimates were odds ratios for case-control studies, relative risks for cohort studies, and the corresponding 95%