Progestogen-Only Contraceptives and the Risk of Stroke
A Meta-Analysis

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Background and Purpose—The association between combined oral contraceptives (OC) use and increased risk of stroke has been reported. While progestogen-only contraceptives (POC) are commonly used worldwide, their impact on cardiovascular disease remains unclear.

Methods—A meta-analysis based on EMBASE and MEDLINE referenced literature corresponding to OCs marketed since 1960 was carried out. Eligible articles assessing the risk of stroke in relation to OC or POC were reviewed, and relevant studies were extracted. All types of POC and routes of administration were taken into account in the meta-analysis.

Results—Six case–control studies were identified. The combined odd ratio (OR) showed no increase in the risk of stroke among POC users (OR=0.96; 95% confidence interval: 0.70 to 1.31). This result was similar according to the route of administration (either implant or injectable or oral POC).

Conclusion—Data from observational studies show that POC use is not associated with an increased risk of stroke. However, these results are based on limited data. Further investigations are needed in women with risk factors of stroke.

Key Words: progestogen-only pill | oral contraceptives | stroke | cardiovascular risk | meta-analysis

Stroke is an uncommon pathology among healthy childbearing age women with an annual incidence increasing with age (6 per million at age 20 to 24, 10 per million at age 30 to 34, and 16 per million at age 40 to 44).1 However cardiovascular disease, including stroke, is an important determinant of the benefit/risk profile of oral contraception. Epidemiological studies regarding the association between stroke and OCs use led to conflicting results.2–9 However, recent meta-analysis concluded that the current use of low-dose OC increased the overall risk of stroke by 2-fold compared with nonuse.10–13 This association increased in presence of migraine, high blood pressure, or smoking.14–16

Although the original development of OC focused on progestogen-only products, progestogen-only contraceptive pills (POCs) were introduced later than combined OC into family planning.17 Thirteen million people worldwide are estimated to be current POC users.18 This contraception might be an attractive alternative for women with or without cardiovascular risk factors. However, because the incidence of stroke among childbearing age women is low and studies are mostly underpowered to detect this end point, data on the association of stroke with POC remain scarce.

Therefore, we conducted a meta-analysis of epidemiological studies to evaluate the relationship between use of POC and risk of stroke.

Materials and Methods

Selection of Studies
All the literature published since the early sixties after the introduction of OC has been reviewed. Potentially eligible articles were identified from MEDLINE and EMBASE using the following heading MESH terms: “stroke,” “cerebrovascular disease,” “cardiovascular disease,” “progestogen-only pill,” “minipill,” and “contraceptives.” We screened all articles identified on their abstracts. We also identified original articles by back references from general reviews. We excluded publications which were not related to the topic, on hormone replacement therapy and biological studies. The selected articles were reviewed and we excluded general reviews and articles that did not assess stroke risk.

Data Extraction
All relevant articles were consensually selected by two investigators (Z.C. and G.P.B.). We assessed the quality of studies using specific checklist, and we only included studies that fully completed these inclusion criteria. Firstly, cohort or case–control studies were included if they were controlled at least for age. All types of strokes, ischemic and hemorrhagic, were taken into account in the meta-analysis. Hemorrhagic strokes were caused by subarachnoid, intracranial, or intraparenchymal hemorrhage. Moreover, contraceptives users and nonusers (never and past users) were clearly defined. POCs included either implant or injectable or oral progestogen.

Statistical Analysis
For each study, we used the most adjusted OR with its 95% confidence interval and we estimated variance of OR from the 95% confidence interval and we estimated variance of OR from the 95% confidence interval and we estimated variance of OR from the 95%
confidence interval. We weighted ORs by the inverse of their variances to obtain a pooled assessment of the OR. The combined OR was obtained using both a fixed effect model\(^1\) and a random effect model\(^2\). In the fixed model, it is assumed that the effect is the same in all pooled studies and that the variations observed between studies correspond only to random measurement errors. On the contrary, the random effect model acknowledges the fact that the variations observed between studies correspond to a combination of a specific true effect and measurement errors. We tested for heterogeneity between the studies by using the Cochrane test. We assessed publication bias graphically by using funnel plot and statistically by using linear regression test of funnel plot asymmetry. We used R statistical software package version 2.4.0 for all analyses.

**Results**

The systematic retrieval process to identify eligible studies is summarized in Figure 1. No cohort assessing POC use and stroke risk was published. We included only 6 case–control studies\(^{18,21–25}\). Characteristics of the included studies are summarized in the Table. Four of them were carried out in Europe\(^{21,22,24,25}\) one in the United States\(^{23}\) and one worldwide\(^{18}\). Stroke was documented and diagnosed with clinical and radiological tools. Three studies dealt with ischemic stroke\(^{22,24,25}\) whereas the others provided data on both ischemic and hemorrhagic strokes\(^{18,21–23}\). Participants’ age in the included articles ranged from 15 to 44 years old, and controls were matched for age. The number of subjects varied across the studies (from 26 to 1828 for cases and from 224 to 5334 for controls). Subjects were exposed to oral POC in 4 studies\(^{21,22,24,25}\) or to oral and injectable POC in another one\(^{18}\) or to Norplant in the last one\(^{22}\). Types of POCs are detailed in the Table. Nonusers included never and former users. Users were defined as taking POCs at the time of the event\(^{21,25}\) or within 122 or 3 months before\(^{24}\). Nonusers were mostly used as the reference group, except in the study by Lidegaard which used never users as the reference\(^{21}\).

The pooled estimated OR for stroke risk associated with oral POC users was 1.00 (95% CI: 0.68 to 1.49; Figure 2). The test for heterogeneity was not significant (\(\chi^2=0.31\) probability value =0.98). For all types of route of administration (oral, implant, and injectable), the combined OR was 0.96 (95% CI: 0.70 to 1.31). When injectable progestogen was excluded, no difference in estimated OR was found. We did not find evidence of publication bias from the funnel plot, which showed a symmetrical distribution of the individual study OR around the overall OR (Figure 3). The linear regression test of funnel plot asymmetry was not significant \((P=0.76)\).

**Discussion**

To our knowledge, this meta-analysis is the first assessing the association between POC and stroke risk. No significant

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**Table. Characteristics of Studies Assessing the Risk of Stroke in Relation to Progestogen-Only Contraceptive Use**

<table>
<thead>
<tr>
<th>Case–Control Study, Year</th>
<th>Region</th>
<th>Years of Study</th>
<th>Age</th>
<th>Control Type</th>
<th>No. of Cases/Controls</th>
<th>No. of POC Users</th>
<th>POC Type</th>
<th>Stroke Definition</th>
<th>Adjusted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidegaard 1993(^{21})</td>
<td>Denmark</td>
<td>1990 to 1991</td>
<td>15 to 44</td>
<td>Population controls</td>
<td>211/1024</td>
<td>7/18</td>
<td>Oral*</td>
<td>All</td>
<td>Age, smoking, education</td>
</tr>
<tr>
<td>Tzourio 1995(^{22})</td>
<td>France</td>
<td>1990 to 1993</td>
<td>18 to 44</td>
<td>Hospital</td>
<td>26/114</td>
<td>1/4</td>
<td>Oral*</td>
<td>Ischemic</td>
<td></td>
</tr>
<tr>
<td>Pettiti 1998(^{23})</td>
<td>USA</td>
<td>1990</td>
<td>18 to 44</td>
<td>Population controls</td>
<td>518/1547</td>
<td>1/3</td>
<td>Norplant(^{2})</td>
<td>All</td>
<td>Age</td>
</tr>
<tr>
<td>WHO 1998(^{18})</td>
<td>Worldwide</td>
<td>1989 to 1993</td>
<td>20 to 44</td>
<td>Hospital</td>
<td>1828/5334</td>
<td>54/151</td>
<td>Oral and injectable(^{2})</td>
<td>All</td>
<td>HBP, smoking, marital status</td>
</tr>
<tr>
<td>Heinemann 1999(^{24})</td>
<td>Europe</td>
<td>1996 to 1993</td>
<td>16 to 44</td>
<td>H and P</td>
<td>90/492</td>
<td>3/10</td>
<td>Oral*</td>
<td>Ischemic</td>
<td>HBP, alcohol, smoking</td>
</tr>
</tbody>
</table>

WHO indicates World Health Organization; H, hospital; P, population controls; All, ischemic and hemorrhagic strokes; HBP, high blood pressure.

*Not detailed. †Continuous low doses of levonorgestrel. \(^*\) Oral POCs: levonorgestrel, ethynodiol diacetate, lynestrenol, norethisterone, anorethidrate dipropionate; injectable POCs: medroxyprogesterone acetate and norethisterone oenanthate both administered monthly or quarterly.
association was apparent between POC and stroke risk with an overall OR of 0.96 (95% CI: 0.70 to 1.31).

This meta-analysis has several methodological limitations. All selected studies were case–control studies, which are susceptible to recall bias contrary to cohort studies. A survival bias could also explain null findings, and we cannot exclude an increased risk of fatal stroke associated with the first year POC use. In addition, the small samples size resulted in a lack of statistical power. Moreover, definition of cases was heterogeneous, and it has not been possible to assess the risk of stroke according to the type (either ischemic or hemorrhagic). Furthermore, the magnitude of the association between POC and stroke could be affected by 2 distinct parameters: (1) the selection of a hospitalized control group (versus a population control group) could underestimated this relationship, and (2) the definition of POC users and nonusers varied from 0 to 3 months before the occurrence of stroke, which could classify a participant into one or the other category depending on each study. Finally, although almost all publications controlled for appropriate confounders, some important other risk factors might be unbalanced between POC users and non users.

Some cardiovascular risk factors could be involved in the association between stroke risk and POC use. The WHO study found an OR of 7.21 (95% CI: 6.10 to 8.52) in hypertensive women which enhanced with POC use (OR=12.4 95%, CI: 4.09 to 37.6), but the authors requested careful interpretation. Moreover, such a synergism between POC use and high blood pressure was not confirmed in the Transnational Study, but the numbers of subjects in the stratified analyses were small.

Similar data regarding smoking were reported in the WHO study. For smokers who did not use any OC, the adjusted OR for stroke was 1.50 (95% CI: 1.28 to 1.75). For POC users, the corresponding OR was 2.47 (95% CI: 0.46 to 13.2).

Lipoproteins have been measured in several studies. Little change in the total cholesterol/HDL cholesterol ratio has been showed which might imply that POC should not aggravate risk factors for atherosclerosis.

A meta-analysis based on observational studies suggested that the risk of stroke was associated with the occurrence of migraine without aura (OR=1.83, 95% CI: 1.06 to 3.15) as well as with aura (OR=2.27, 95% CI: 1.61 to 3.19). This association increased with OC use (OR=8.72, 95% CI: 5.05 to 15.05). Unfortunately, no additional analysis was available to estimate whether or not POCs could be involved in the migraine related risk of stroke.

POC seems to have probably no deleterious effect on hemostasis. Indeed, Winkler et al showed that desogestrel and levonorgestrel induced a decrease in factor VII activity and fragment 1, whereas antithrombin and protein C remained stable. Moreover, a phase III trial focusing on injectable contraception reported a decrease in both C-reactive protein (CRP) and D-dimer, which suggested no impact of POC on risk of venous or arterial thrombosis. Some studies reported a link between high CRP levels and the risk of myocardial infarction or stroke. Likewise D-dimer is a marker of procoagulant and subsequent fibrinolytic activity, which was established as an indicator of venous and sometimes arterial thrombotic risk. Studies have reported no increase of venous thromboembolic risk with POC use.

Medical practice regarding POC use could explain in part the null findings observed in our meta-analysis. In the
Transnational study, POC users tended to be older, had a higher body mass index, were more often smokers, suffered more frequently from hypertension, and were more likely to report a family history disease of stroke than users of combined oral contraceptives.24 Some of these differences in the risk factor profile were also observed in the WHO study.18 In fact, this latter study included a large population from developing countries where POC are frequently prescribed as first line because of their cheapness and effectiveness, whereas they are often used as an alternative to OCs among women with cardiovascular risk factors in industrial countries. Another explanation could be that these women are narrowly monitored to correct these cardiovascular risk factors. According to this literature, POCs are authorized by the WHO recommendations on contraception strategy for women with cardiovascular risk factors.36 Nevertheless, no study has been published on the impact of POC use in women with personal history of stroke or in women with arterial risk factors.

In conclusion, this meta-analysis suggests that POC use might be safe with respect to stroke risk. However, further investigations on the impact of POC use on the risk of stroke among women with cardiovascular risk factors are needed. POC use in these women must be cautious.

Disclosures

None.

References


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