Ischemic Stroke Risk in Oral Contraceptive Users

To the Editor: We read with interest the article by Siritho et al on ischemic stroke risk in oral contraceptive users.1 This case-control study seems well conducted, but the conclusion is not consequent to the results obtained. The conclusion of a study is of crucial importance when it deals with the practical implication of the study itself, which, in the case in point, is done to reconsider the current recommendations that restrict the use of the oral contraceptive pill (OCP) to younger women who do not have other risk factors for cardiovascular disease.2 The authors in their conclusion “recommend that the OCP (in low doses) be prescribed with care” and add that “particular care should be taken among women with a history of smoking, hypertension, diabetes mellitus, and myocardial infarction and in those with a family history of stroke.” 3 This conclusion, in discordance with the study results, deserves some considerations:

1. The principle that OCP, as any other drug, must be prescribed with care is a good and notorious one but it has not been shown in the present case-control study, which did not find any evidence for an association between ischemic stroke and OCP use.

2. It is not clear what the authors mean by “particular care” in prescribing OCP to patients with risk factors for cerebrovascular diseases. Rather, the authors do not answer the real question on whether to prescribe or not to prescribe OCP in “women with a history of smoking, hypertension, diabetes mellitus, and myocardial infarction and in those with a family history of stroke.”

3. This article shows that OCP in low doses does not increase the risk of stroke in women with risk factors for cardiovascular disease. Therefore, the practical implications should have indicated that the presence of smoking, hypertension, diabetes mellitus, and myocardial infarction and a family history of stroke should not discourage from prescribing OCP when the alternative is a risky and undesired pregnancy.

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First, the results of this study should not be taken in isolation. Our results contrast with those of numerous other investigations of the role of the OCP in stroke, as provided in a recent meta-analysis.3 In these other investigations the summary odds ratio for the OCP and ischemic stroke was approximately 2. Although in our study the risk of ischemic stroke with OCP use was 1.76, the 95% confidence intervals in this study could not exclude odds ratios of about 3. Because of the available evidence for an association between OCP use and ischemic stroke, we cannot exclude the previous evidence, despite our findings.

Second, the OCP has been implicated in other disease conditions, such as deep venous thrombosis. The combined effect of these agents on all diseases needs to be considered when making changes to its prescription.

Third, one must keep in mind that case-control and cohort studies are subject to numerous biases. Although we made every attempt to reduce the possibility of bias, it is still possible that bias has affected the results. One of the biases that is difficult to control for is that of recall. It is possible that women may have recalled the use of the OCP imperfectly. This is particularly so because of the many changes in the content of the OCP over time. In addition, this recall may have been more imperfect in the women with stroke as there may have been some stroke-related memory problems. This would have biased the results toward the null.

Finally, our study was conducted at a time when second-generation OCPs were predominantly being prescribed. Although there was considerable evidence for a stroke risk among women using high-dose preparations, there was little information on the impact of the newer low-dose treatments. Because we were interested in investigating whether or not use of these lower-dose treatments was associated with stroke, we collected data on whether the preparations contained ethinylestradiol in doses above or below 50 μg. We did not, however, collect information on the actual doses of the agents prescribed, or on the other hormones also contained in each pill. It is possible that these factors were imbalanced between groups. As we have been unable to account for this in the analysis, we may have missed an association that was indeed present.

In conclusion, although it would have been advantageous to be able to reconsider the current guidelines for the prescription of the OCP, we think that this would have been premature given the discordance with other study results, the fact that the OCP has impact on other diseases, and the potential biases that may have existed. Clearly, more data on this subject are required before quite definitive statements can be made. We have, therefore, adopted a cautious approach in our recommendations in the interim.

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Response  

Drs Ciccone and Melis raise an important point about the use of study results to reconsider current guidelines.1 As they have mentioned, current guidelines restrict the use of the oral contraceptive pill (OCP) to younger women who do not have other risk factors for cardiovascular disease. We agree that, when viewed in isolation, our study results might not agree with these guidelines.2 However, these results should be viewed using a wider framework.

First, the results of this study should not be taken in isolation. Our results contrast with those of numerous other investigations of the role of the OCP in stroke, as provided in a recent meta-analysis.3 In these other investigations the summary odds ratio for the OCP and ischemic stroke was approximately 2. Although in our study the risk of ischemic stroke with OCP use was 1.76, the 95% confidence intervals in this study could not exclude odds ratios of about 3. Because of the available evidence for an association between OCP use and ischemic stroke, we cannot exclude the previous evidence, despite our findings.

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