Headache
© 2006 by American Headache Society
Published by Blackwell Publishing

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2006.00347.x

Expert Opinion

Migraine and Oral Contraceptives

Case History Submitted by Randolph W. Evans, MD
Expert Opinion by Werner J. Becker, MD

(*Headache* 2006;46:328-331)

There are many uncertainties in the use of oral contraceptives (OCs) in migraineurs.

CLINICAL HISTORY

A 27-year-old female was referred by her primary care physician for acute and preventive migraine medications. She has a history of migraine since the age of 14. For the last 2 years, she has migraine without aura about twice a week. About three times a year, she has a visual aura lasting 20 to 30 minutes followed by a similar headache. She has been on low estrogen dose OCs for 8 years.

Questions.—Because of her occasional migraine with aura, should she continue the OCs? What is the relative and absolute risk of stroke for patients with migraine with aura on low estrogen OCs and off? In defining this risk, are there subpopulations with different risks such as migraine with aura rarely versus frequently or those with prolonged aura? Is there any data to suggest a benefit from continuing OCs and also taking daily aspirin? If a patient has nonspecific white matter abnormalities on an MRI scan, does this change the approach?

Address all correspondence to Dr. Randolph W. Evans, 1200 Binz #1370, Houston, TX 77004, or Werner J. Becker, MD, University of Calgary, Foothills Hospital, Division of Neurology, 12th Floor, 1403 29th Street NW, Calgary, Alberta T2N 2T9, Canada.

EXPERT COMMENTARY

Migraine is three times as common in women as in men, and often starts in the teens or twenties. Migraine, then, often coexists with a need for effective contraception.

Concern over the use of OCs in women with migraine arises because both migraine and the use of OCs are proven stroke risk factors. For migraine, the increased stroke risk involves primarily ischemic stroke. Fortunately, the most common type of migraine, migraine without aura, carries relatively little increased stroke risk. Odds ratios found for ischemic stroke risk for women with migraine without aura as compared to nonmigraine controls have ranged from 1.5 to 3.0.[1] A recent meta-analysis of 14 studies has settled on an overall increased relative risk of 1.8 (95% CI 1.1 to 3.2) for migraine without aura.[2] Once these migraineurs become older (over age 45), an increased ischemic stroke risk is no longer demonstrable.[3,4]

Ischemic stroke risk is greater for women with migraine with aura. In younger women, odds ratios for this increased stroke risk have ranged from 3.8 to 6.2.[1] For migraine with aura, overall the relative risk of ischemic stroke appears to be increased to 2.3 (95% CI 1.6 to 3.2).[2] In older women with migraine with aura (over age 45), ischemic stroke was increased as compared to nonmigraine controls with a hazard ratio (adjusted) of 1.73.[4] In another study which included

both women and men over age 45, the odds ratio for ischemic stroke risk, migraine with aura versus controls, was 2.07.[3]

Use of OCs also brings significant stroke risk, although this risk depends on the estrogen content of the OCs, and likely also on what other risk factors for stroke the patient may have. While OCs with 50 μg of estrogen or more have been reported to have significant stroke risk with odds ratio as high as 5.3, the evidence suggests that low estrogen dose OCs (<50 μg) carry little or no stroke risk, at least as prescribed in Europe and the United States.[5] A recent meta-analysis indicated a relative risk for ischemic stroke of 4.5 (95% CI 2.2 to 9.5) for OCs with more than 50 μg of estrogen, and 2.1 (95% CI 1.6 to 2.8) for OCs with less than 50 μg.[6] There is controversy, however, and a recent Australian study[7] and an American study[8] were unable to show an increased risk of ischemic stroke in women on low dose OCs.

How do all these research findings relate to our patient? She has relatively frequent attacks of migraine without aura, but these are likely not a major concern with regard to oral contraception, as any increase in stroke risk is likely to be small. There is always the possibility that her OCs are exacerbating her migraine, and a trial of at least several months off OCs would be advisable to assess this. If her attacks diminish in frequency, then she should not resume OCs. Of more concern are her attacks of migraine with aura. These are relatively infrequent, and consist of typical visual symptoms with the usual duration. Nevertheless, at her age, they probably indicate an increased ischemic stroke risk of approximately three- or fourfold as compared to a woman without migraine.

How do OCs interact with this increased risk? Here, our ability to use data starts to fade. Very high ischemic stroke risks have been reported in migrainous women on OCs,[9,10] but these were based on very small sample sizes, and some women were using OCs with high estrogen content. Migraine with aura increases baseline stroke risk, and so it would be expected that OCs might result in a greater absolute increase in ischemic stroke risk in women with migraine with aura as compared to controls.[6] However, this increase in stroke risk might not be as large as once thought, particularly with low estrogen OCs.

The absolute ischemic stroke risk for young women between age 25 and 30 is very low, approximately 3/100,000 women per year.[11,12] If migraine with aura triples this stroke risk, then our patient may have a basal stroke risk of 9/100,000 women per year. Her low dose OCs likely increase this ischemic stroke risk further, probably by a factor of approximately 2, giving her an overall ischemic stroke risk of 18/100,000 women years. These figures are obviously approximations. To put all these in practical terms, if she were to stay on her low dose OCs for another 5 years, her likelihood of having an ischemic stroke during that time would be slightly less than 1 in 1000. That is, one would expect approximately one ischemic stroke in 1000 women like her who stayed on low dose OCs for 5 years. The question is whether this risk compares favorably to the risks of unwanted pregnancies and perhaps therapeutic abortions.

In an ideal world, our patient should not be on OCs because of her migraine with aura. She should explore other methods of contraception which do not carry a stroke risk. It must be recognized that several professional bodies have produced guidelines or stated that patients like her should not be on OCs. While the benefits of OCs are felt by most organizations to usually outweigh the risks for patients with migraine without aura who are under age 35, some (American College of Obstetricians and Gynecologists, World Health Organization) indicate that the risk of OCs is unacceptable if women with migraine have focal symptoms.[13]

On a practical level, many family physicians do prescribe low dose OCs for women with migraine with aura. Several neurologist headache experts have also published the view that when it comes to migraine with typical aura and OCs, individualized decision making is called for.[5,13]

For our patient, a 27-year-old otherwise healthy woman with migraine with aura, I would favor individualized decision making. She must be informed that her use of OCs is increasing her ischemic stroke risk. Although the magnitude of this increased risk is likely a doubling of her baseline stroke risk, this risk is still relatively small in absolute terms. All these factors need to be discussed, and she owes it to herself to discuss alternative contraception options with a physician knowledgeable in this area. If she is

hypertensive, obese, or a smoker, she should not be on OCs. If none of these apply to her, she should still attempt to reduce her stroke risk further by regular exercise. The bottom line is, however, that I would not consider her migraine with aura to be an absolute contraindication to use of OCs, and I believe this also reflects current practice by most clinicians on the front lines. For each patient, the risks and benefits need to be considered, and for many, OCs offer many benefits.

Should our patient have auras beyond the usual, for example, auras longer than 30 to 45 minutes, or auras with weakness or speech disturbances, I would strongly recommend that she stops her OCs. The same would apply if her auras were typical but frequent to the point of 2 or more per month. We are of course going beyond the evidence here, but discretion is the better part of valor. Despite the lack of data, caution would reasonably suggest the possibility that OCs might contribute a higher risk in these situations. Should she merely have some brief numbness and tingling with her visual symptoms, I would consider this less of a concern, as after visual symptoms, somatosensory symptoms are the second most common aura symptom.

Similarly, there is no direct evidence that aspirin prophylaxis reduces the stroke risk related to her migraine with aura and use of OCs. Aspirin has been shown to reduce ischemic stroke rates in women over age 45 when used for primary stroke prevention (relative risk 0.76; 95% CI 0.63 to 0.93).[14] Our patient is in a very different age range, however, and has specific stroke risk factors. I would not rely on or use aspirin long term in a theoretical attempt to mitigate her stroke risk while on OCs. Conversely, given the favorable side effect profile of low dose aspirin, if she had developed unusual aura symptoms while on OCs, I would consider using aspirin short term while the OCs were being discontinued.

Women with migraine have a higher likelihood of having silent white matter subcortical hyperintensities on brain MRI scanning than those without migraine.[15,16] The cause of these white matter hyperintensities is not known, and nor is their pathology. In elderly people, individuals with subcortical white matter lesions have been found to have a higher risk of stroke even after adjustments for known stroke risk factors.[17] The relevance of these findings in elderly patients to young migraine patients with white matter hyperintensities is unclear. Should our 27-year-old patient with migraine with aura have 5 or 6 small white matter hyperintensities on MRI scan, I would be inclined to recommend more strongly that she stops her OCs, although there is really no good evidence to support this action. The white matter hyperintensities likely do have a vascular origin, and so this action seems prudent. Because of the tenuous nature of this advice, I would not specifically order an MRI scan in a patient like this in order to help with this decision making.

More good research is needed to enable us to give better advice to our patients. In the meantime, we are left with indirect evidence and our best judgment. While it is important to be cautious, it is also important not to deny patients useful medications like OCs because of unwarranted fear and speculation based on indirect evidence. Fortunately, most of our patients are intelligent, and can with our help review the facts as they are known, and help make a decision based on their personal needs and values.

REFERENCES

1. Tzourio C, Kittner SJ, Bousser M-G, Alpérovitch A. Migraine and stroke in young women. *Cephalalgia.* 2000;20:190-199.
2. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: Systematic review and meta-analysis of observational studies. *BMJ.* 2005;330:63.
3. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, et al. Headache, cerebrovascular symptoms and stroke—The Atherosclerosis Risk in Communities Study. *Neurology.* 2005;65:1573-1577.
4. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache and the risk of stroke in women—A prospective study. *Neurology.* 2005;64:1020-1026.
5. Bousser M-G, Kittner SJ. Oral contraceptives and stroke. *Cephalalgia.* 2000;20:183-189.
6. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives. *JAMA.* 2000;284:72-78.

7. Siritho S, Thrift AG, McNeil JJ, You RX, Davis SM, Donnan GA. Risk of ischemic stroke among users of the oral contraceptive pill—The Melbourne Risk Factor Study (MERFS) Group. *Stroke.* 2003;34:1575-1580.
8. Schwartz S, 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.* 1998;29:2277-2284.
9. Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case–control study of migraine and risk of ischaemic stroke in young women. *BMJ.* 1995;310:830-833.
10. 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.* 1999;318:13-18.
11. Petitti DB, Sidney S, Quesenberry CP, Bernstein A. Incidence of stroke and myocardial infarction in women of reproductive age. *Stroke.* 1997;28:280-283.
12. Becker W. Use of oral contraceptives in patients with migraine. *Neurology.* 1999;53(suppl 1):S19-S25.
13. Loder EW, Buse DC, Golub JR. Headache and combination estrogen–progestin oral contraceptives: Integrating evidence, guidelines, and clinical practice. *Headache.* 2005;45:224-231.
14. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352:1293-1304.
15. Swarz R, Kern R. Migraine is associated with MRI white matter abnormalities: A meta-analysis. *Arch Neurol.* 2004;61:1366-1368.
16. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA.* 2004;291:427-434.
17. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and white matter lesions increase stroke risk in the general population—The Rotterdam Scan Study. *Stroke.* 2003;34:1126-1129.