

## CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

## Oral Contraceptives for Menstrual Migraine with Aura

*This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.*

## CASE VIGNETTE

**A Patient with Chronic Migraines**

Clement D. Lee, M.D.

A 30-year-old woman who has chronic migraines comes to the clinic to discuss her headaches. Since adolescence, she has had migraine headaches, marked by unilateral throbbing cranial pain with nausea and photophobia, that have occurred 10 to 12 times a year. The headaches are usually preceded by the sensation of shimmering lights that migrate across her visual field. Her current medications include topiramate (once daily), propranolol (twice daily), and oral sumatriptan to abort acute attacks. She does not smoke tobacco or use electronic cigarettes. There is no history of cardiovascular disease in her family.

The patient's vital signs are normal, and the results of the physical examination are unremarkable. She has previously been instructed to document her headaches in a journal, and she has noticed that they frequently occur around the time of her menses. She has no desire for pregnancy and inquires about the use of a combined oral contraceptive pill for the management of her migraines and for contraception.

The patient's physician consults with you and asks you to advise whether combined (estrogen–progestin) oral contraceptive pills should be prescribed for this patient with mainly catamenial migraine with aura to reduce the frequency of migraine attacks.

## TREATMENT OPTIONS

Which one of the following approaches would you take? Base your choice on the literature, your own experience, published guidelines, and other information.

1. Recommend prescription of combined oral contraceptive pills.
2. Do not recommend prescription of combined oral contraceptive pills.

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

From the Departments of Medicine and Pediatrics, Tufts University School of Medicine, Boston.

## OPTION 1

**Recommend Prescription of Combined Oral Contraceptive Pills**

Rossella E. Nappi, M.D., Ph.D.

Both the U.S. and World Health Organization medical eligibility criteria for contraceptive use list migraine with aura as an absolute contraindication to combined oral contraceptives.<sup>1</sup> The estrogen component of modern combined oral contraceptives has been implicated in augment-

ing the risk of ischemic stroke associated with migraine with aura. Women who have migraines with aura have twice the risk of stroke as women without migraines (5.9 vs. 2.5 events per 100,000 persons annually), and the risk is nearly six times as great with contraceptive use (14.5 events per 100,000 persons).<sup>2</sup> Even though the overall absolute risk of stroke is low, stroke can cause serious complications, and other hormonal options (e.g., progestogen-only contraception) are available. Both the American Headache Society and the International Headache Society are less definitive about the contraindication of oral con-

traceptives and recommend an individualized decision with respect to oral contraceptives that is based on benefits and risks, especially in the absence of other risks factors for stroke, such as an age older than 35 years, tobacco use, hypertension, obesity, diabetes, or hyperlipidemia.<sup>3</sup>

Providing effective contraception in a woman such as the one described here requires obtaining a detailed clinical history. The woman in the vignette is taking two prophylactic migraine medications (an antiepileptic drug and a beta-blocker) and reports menstrually related migraine (i.e., migraine broadly related to menstruation but not limited to the days during menstruation) with visual aura that responds to sumatriptan, which belongs to a third class of antimigraine medications. Although aura associated with menstruation is not common, it does occur and, when present, is usually associated with severe, prolonged migraines that are refractory to both prophylactic medications and medications to treat symptoms.<sup>4</sup>

Therefore, the patient's request for a combined oral contraceptive pill, the most common form of hormonal contraception, to control her migraines is legitimate and should not be automatically discounted on the basis of presumed stroke risk in the absence of substantial risk factors. Available data do not support the use of these agents to prevent general migraines, but avoidance of fluctuations in estrogen levels may help manage menstrually related migraines effectively; estrogen-containing pills are also useful in many menstrually regulated reproductive conditions (e.g., heavy menstrual bleeding or dysmenorrhea).<sup>4,5</sup> It would be pertinent to determine the dose of topiramate prescribed to this patient, since daily doses higher than 200 mg may reduce contraceptive potency.<sup>6</sup>

Combined oral contraceptives with continuous, extended, or flexible regimens; short hormone-free intervals; or supplementation with estrogen alone during the hormone-free interval may reduce menstrual bleeding and make migraines more predictable in women with menstrually related migraines.<sup>4,5</sup> Low-dose estrogen can be used even in women who have simple visual aura, with careful monitoring and discontinuation if the auras worsen. Preparations containing very low doses of estrogen (e.g., 10 to 20  $\mu\text{g}$  of ethinyl estradiol) are not clearly linked to the risk of stroke, as compared with the higher

doses (e.g., 30 to 50  $\mu\text{g}$ ) investigated in earlier studies.<sup>5</sup> New formulations with alternative routes of administration (e.g., intravaginal) may expose a woman to low stable doses of ethinyl estradiol that have less effect on the body but still deliver levels of hormones that can block ovulation.<sup>4,5</sup>

Finally, a new era of contraception is being heralded by natural estrogens, including 17 $\beta$ -estradiol, estradiol valerate, and estetrol (a native estrogen of fetal origin). These show promise for conferring a lower risk of cardiovascular complications than that associated with ethinyl estradiol and thus may become the most suitable options in women with migraine who need or want combined hormonal contraception.<sup>4</sup>

Disclosure forms provided by the author are available with the full text of this article at [NEJM.org](http://NEJM.org).

From the University of Pavia Medical School, Unit of Reproductive Medicine, IRCCS San Matteo Hospital, Pavia, Italy.

---

## OPTION 2

### Do Not Recommend Prescription of Combined Oral Contraceptive Pills

Carrie Cwiak, M.D., M.P.H.

Combined oral contraceptives are the most common method of reversible contraception in the United States.<sup>7</sup> However, there are several alternative hormonal and nonhormonal contraceptive methods available. Patient-centered contraceptive counseling requires ensuring that each patient is aware of all contraceptive options, including the characteristics, benefits, and risks of each method in the context of needs, values, and preferences, so that the patient can make an informed decision. In this situation, the clinician should ask the patient whether her utmost priority is to decrease the frequency of migraine headaches or to avoid pregnancy. Are her current migraine medications suboptimal owing to side effects or limited access? Does she desire pregnancy at any time in the future? What are her preferences for contraceptive use requirements or expected bleeding patterns? The relevant benefits and risks of the various options are important for the patient to consider.

Attention to the timing of migraines that occur around the time of menses may elucidate whether they are related to estrogen withdrawal

before menses, prostaglandin release during menses, or both.<sup>8</sup> Since all systemic hormonal contraceptive methods inhibit ovulation and suppress menses, their use may decrease the frequency or severity of menstrual migraines. The progestogenic component in all systemic hormonal contraceptive methods is responsible primarily for inhibiting the luteinizing hormone surge, ovulation, and menstrual bleeding. Systemic progestin-only contraceptives include the subdermal implant, injectable contraceptives, and progestin-only oral contraceptives. The estrogenic component added to combined agents provides the option for cyclic bleeding that mimics a menstrual pattern; this component is also found in transdermal patches and vaginal rings.<sup>8</sup> It is the estrogenic component that increases the risk of cardiovascular events (e.g., venous thromboembolism, myocardial infarction, or stroke) in users of combined hormonal contraceptives.

The baseline risk of stroke in women of reproductive age is only 5 to 10 cases per 100,000 woman-years.<sup>8</sup> The risk of ischemic stroke is increased in patients with migraines, and more so if aura is present. A systematic review of studies involving users of combined oral contraceptives who have migraines showed that the risk of stroke was two to four times that in nonusers with migraines.<sup>9</sup> Included was a study that evaluated the association of the use of these drugs with the risk of stroke according to migraine type, which showed an increased risk of stroke only among users with migraine with aura as compared with users without migraine (odds ratio, 1.5; 95% confidence interval, 1.1 to 2.0).<sup>10</sup> This prompted the Centers for Disease Control and Prevention to assert that combined hormonal contraceptives may be used by patients who have migraines without aura, but among those who have migraines with aura, their use presents an unacceptable health risk.<sup>1</sup> In contrast, patients who have migraines with aura can safely use progestin-only and nonhormonal contraceptive methods.<sup>1</sup> Although data are lacking from studies on progestin-only contraceptive use in patients with migraines, in an international case-control study, no increased risk of cardiovascular events was observed among healthy users of progestin-only oral or injectable contraceptives.<sup>11</sup> With the availability of lower-risk alternatives for menstrual suppression, there is no

compelling reason to offer a combined hormonal contraceptive pill to this patient.

Finally, although hormonal contraception has benefits related to ovulation inhibition and menstrual suppression, it is not a first-line therapy for control of migraines regardless of whether they are related to menses. Other migraine therapies, including newer agents such as calcitonin gene-related peptide receptor antagonists (gepants), should be considered, and separately, locally acting intrauterine devices and barrier methods should still be considered for their contraceptive attributes, especially since their use will not affect this patient's risk of cardiovascular or stroke events, nor, contrary to popular belief, will it worsen migraines.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta.

1. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016;65:1-103.
2. Sacco S, Merki-Feld GS, Aegidius KL, et al. Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). *J Headache Pain* 2017;18:108.
3. Sheikh HU, Pavlovic J, Loder E, Burch R. Risk of stroke associated with use of estrogen containing contraceptives in women with migraine: a systematic review. *Headache* 2018;58:5-21.
4. Nappi RE, Tiranini L, Sacco S, De Matteis E, De Icco R, Tasorelli C. Role of estrogens in menstrual migraine. *Cells* 2022;11:1355.
5. Calhoun AH. Hormonal contraceptives and migraine with aura — is there still a risk? *Headache* 2017;57:184-93.
6. Viana M, Terreno E, Goadsby PJ, Nappi RE. Topiramate for migraine prevention in fertile women: reproductive counseling is warranted. *Cephalalgia* 2014;34:1097-9.
7. Daniels K, Daugherty J, Jones J, Mosher W. Current contraceptive use and variation by selected characteristics among women aged 15–44: United States, 2011–2013. *Natl Health Stat Report* 2015;86:1-14.
8. Cwiak C, Edelman AB. Combined oral contraceptives. In: Hatcher RA, ed. *Contraceptive technology*. 21st ed. Ayer Company Publishers, 2018:265-316.
9. Tepper NK, Whiteman MK, Zapata LB, Marchbanks PA, Curtis KM. Safety of hormonal contraceptives among women with migraine: a systematic review. *Contraception* 2016;94:630-40.
10. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the Stroke Prevention in Young Women study. *Stroke* 2007;38:2438-45.
11. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives: results of an international, multicenter, case-control study. *Contraception* 1998;57:315-24.

DOI: 10.1056/NEJMcld2303811

Copyright © 2023 Massachusetts Medical Society.