

Is it time to rethink the use of oral contraceptives in premenopausal women with migraine?



SPEAKERS:

Interviewer—Janelle Yates, Senior Editor, OBG MANAGEMENT

Interviewee—Anne H. Calhoun, MD

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PART 1 Data dissection

- Migraine versus migraine with aura versus tension headache
- Baseline risk of stroke in patients with migraine
- What does the literature suggest about the risk of stroke associated with combination oral contraceptives (OCs) in women with migraine?
- What have been the objections in the past to OC use in women with migraine?

Janelle Yates: This is Janelle Yates, Senior Editor of OBG MANAGEMENT. Dr. Anne Calhoun sometimes jokes that she's a neuro-gynecologist, or a gynecologic neurologist, a reference to her expertise in managing both the neurologic and hormonal aspects of menstrual migraine. In reality, she's a headache specialist, a partner and cofounder of the Carolina Headache Institute in Chapel Hill, North Carolina, and a professor in the Departments of Psychiatry and Anesthesiology at the University of North Carolina, Chapel Hill. In this in-depth two-part interview, Dr. Calhoun explains how oral contraceptives (OCs) can actually help women with migraine. In Part 1, she defines migraine, with and without aura, and dissects the data on OCs and stroke, and OCs and migraine. In the process, she explains why, in the setting of migraine, she thinks ACOG's last practice bulletin on the use of hormonal contraception in women with coexisting medical conditions needs to be updated to reflect the low-dose oral contraceptive formulations widely used today.

In Part 2 of the interview, she explains the benefits of OCs for some women with migraine, explains how she chooses an OC

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Dr. Calhoun reports receiving research support from ElectroCore and GlaxoSmithKline, serving as a speaker for Nautilus Neurosciences and Zogenix, and consulting to Allergan, Nautilus, and Zogenix.

formulation and regimen, and tells why she thinks ObGyns are in a unique position to help women with headaches.

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Dr. Calhoun, how did you come to be a headache specialist?

Dr. Calhoun: It goes back many years ago when I saw a patient whose chief complaint was headache, with a duration of symptoms of 11 years. And, of course, she was scheduled for a 10-minute appointment. She was only 27 years old and was taking 22 different medications! I didn't know where to start, so I said, "Let's just stop all these medicines, then come back, make an appointment for an hour, and let's get to the bottom of this." She came back about a month later and was glowing. She said, "You're a genius, my headaches are gone!" and all I had done was tell her to stop the things she was taking, none of which were essential. Many of her medicines were prescribed to fight the side effects of the others. What I had unconsciously done was cure her of medication-overuse headache (which was not commonly appreciated in the 1970s.) We now know that the overwhelming majority of patients presenting to headache clinics have medication-overuse headache—due to overusing their acute therapies.

JY: Before we go into a more extensive discussion of migraine, why don't we start with a few definitions? Could you define what migraine is? And menstrual migraine? And migraine with aura?

Dr. Calhoun: Yes. A very important issue, since most migraineurs don't know that they have migraine. Obviously, they know they're having headaches, but they typically call it whatever their parents called theirs: sinus headache, stress headache, sick headache, menstrual headache.

By ICHD-2 [International Classification of Headache Disorders, 2nd edition] criteria, migraine pain has to meet two of four criteria:

- one-sided

- throbbing
- made worse with activity
- at least a 4 on a scale of 1 to 10 (moderate to severe levels).

In addition, migraine must include at least one of two associated symptoms:

- nausea with attacks
- preference to avoid bright lights and loud noises during the headache.¹

Patients often erroneously think that migraine means incredibly severe headache. It doesn't. Migraine can be mild or moderate and still technically meet those criteria. But these are headaches that have a propensity to turn ugly.

If you see a headache that puts a patient out of the game—missing work or having to lie down with it—you're probably looking at migraine. The other disabling primary headache ("primary" meaning that it's not secondary to some other underlying condition) is cluster, and in women, migraine is roughly 1,000 times more common than cluster—which is rare to begin with and occurs mostly in men.

Menstrual migraine also has established research criteria: it's migraine without aura that occurs in a window spanning 5 days—beginning 2 days before the onset of bleeding through the third day of flow. Research has shown that menstrual migraine is more severe, longer lasting, and more likely to be disabling (with missed work) than migraine brought on by other triggers.

Migraine with aura is a migraine that is accompanied by a complex neurologic phenomenon called aura. Aura typically lasts 5 to 20 minutes, but no more than 60 minutes. Just as many migraineurs don't know that they have migraine, many patients who think they have aura are describing symptoms that don't meet ICHD-2 criteria.

The most common aura is visual. It reflects an electrochemical wave that moves across the visual cortex and can be captured on functional MRI. The best-known visual aura is the fortification spectrum, which may start as a small hole of light or bright geometrical lines that expand into a sickle- or C-shaped object, with zigzag lines on the leading edge. Auroras may also include a partial loss of vision surrounded by bright shimmering borders, referred to as scintillating scotomas.

The second most common aura is sensory—which is often experienced in conjunction with visual aura. Sensory auras typically begin with tingling or numbness in one hand that then spreads to the same-side elbow and then to the same side of the face and tongue—also lasting about 20 to 30 minutes.

Dysphasic aura causes transient speech or language problems. And rarest of all is a motor aura—also called hemiplegic migraine—in which the patient experiences motor weakness.

Most patients with migraine never have aura. Only 15% to 25% will ever experience one. And when they do, it might occur as infrequently as once or twice a lifetime or as often as several times a month. Most of my patients with aura also have common migraine—or migraine without aura.

JY: What causes migraines?

Dr. Calhoun: Back when I was in training, and we're going back to the 70s here, we were taught that it was a "vascular headache," meaning that the pain was caused by a vascular dilation, and the aura that preceded it was caused by vascular constriction. We now know that this is not correct. Vasodilatation may play a part in the throbbing head pain, but it is probably an epiphenomenon, resulting from instability in the central neurovascular control mechanism.

The mechanism of migraine appears to be primarily neuronal—a dysfunction that leads to a sequence of changes that result in an imbalance in activity between brainstem nuclei that regulate pain and vascular control, excitation and inhibition.

When the trigeminal nerve fibers that line the dural blood vessels are activated, there is a release of kinins, substance P, calcitonin gene-related peptide, and other vasoactive polypeptides that cause pain and vasodilatation and lead to something called "neurogenic inflammation." It makes the brain look like a sterile encephalitis.

I make it simpler for patients. When they ask why they have migraine, I say that the only prerequisite for migraine is inheriting a threshold for setting off the trigeminal nerve that's set too low. Theirs is low enough that things such as estrogen falling before a period, a weather front moving through, somebody wearing the wrong perfume, not getting enough sleep—can all set it off and trigger migraine. Their next-door neighbor with a normal threshold never gets a headache from one of those "migraine triggers."

JY: Do many women who report migraines actually have something else instead, like a tension headache?

Dr. Calhoun: Typically it's the other way around. In fact, Roger Cady did a brilliant study several years ago. He advertised in the *St. Louis Post-Dispatch* for people with "sinus headaches" to come in for a study. Well, what they didn't know is that the study was simply to be interviewed by headache specialists using formal diagnostic criteria to see what kind of headache they actually had. More than 90% of them had migraine.²

Tension-type headache is very common. What's distinctly not common, though, is to seek medical attention for a tension headache—to even mention it to your doctor.

By ICHD-2 criteria, tension headache is diagnosed by the opposite of the criteria used to diagnose migraine. It can be bilateral, steady, not worsened by activity, or mild to moderate in intensity. It needs to meet two out of those four criteria.

The problem is—both migraine and tension-type headache are judged by the same four criteria, and each only has to score two of them. Suppose you have a tie. Say, the headache is steady, bilateral (sounds like tension type), but it's moderate to severe and made worse by moving the head around (sounds like migraine). The tie-breaker comes down to the associated symptoms: Does the patient have nausea? Or does she prefer to avoid bright lights and loud noises with the headache?

The simple version of this is that migraine is an episodic

disabling headache. It is very common in all cultures. Twelve percent to 13% of Americans have migraine, and at midlife, say 30s to 40s, between a quarter and a third of women have migraine.

JY: What does the literature suggest about the baseline risk of stroke associated with migraine?

Dr. Calhoun: All in all, the stroke risk is roughly doubled in migraine. But most if not all of the increased risk is attributable to aura. The migraine-without-aura patient probably has no higher stroke risk than her next-door neighbor. Aura confers the increased risk. In fact, a couple of studies have suggested that the more frequent the aura, the greater the risk of stroke.

JY: What is a relationship between estrogen levels and migraine, including migraine with aura?

Dr. Calhoun: Menstrual migraine occurs in the majority of women with migraine. For them, a sufficient decline in estrogen can trigger a migraine. This can occur with the woman's natural cycle, or following estrogen withdrawal on an oral contraceptive.

The problem is not how high the estrogen goes, it's how far it drops. Studies that I did about 15 years ago showed that if I limited the drop to the equivalent of 10 µg of ethinyl estradiol (EE), I prevented the migraine.³ Back then, this could not be done with any of the OCs as they were packaged. I did this experimentally by using an OC containing 20 µg EE, and adding back 10 µg during the placebo week (similar to a Mircette without the two placebo pills). Obviously, though, using that strategy long-term might present problems. A long pill-free interval with a very low-dose pill can allow ovulation. (We use other strategies now!)

JY: What does the literature suggest about the risk of stroke associated with combination oral contraceptives in women with migraine?

Dr. Calhoun: The use of OCs has been controversial in the setting of migraine with aura due to international studies that showed a small, but increased, risk of stroke with their use. The assumption was that if migraine with aura doubled the risk of stroke, and OCs also increased the risk, then both together might present an unacceptable risk.

A *JAMA* article in 1975 did show an increased stroke risk with OCs—roughly fourfold increased risk (but, interestingly, the risk was no greater in migraineurs than in nonmigraineurs).⁴ Furthermore, the authors could make no correlation between estrogen dose and stroke risk because 23 of the 25 women with thrombotic stroke were taking the 100-µg mestranol formulation, and all 20 of them on EE formulations were taking a 50-µg dose. So these were all high-dose pills. Back in the 70s, that's what we were dealing with. And more recent studies confirm that 50-µg pills still present about a fourfold increased risk of stroke.

Twenty years later, Petitti (in the *New England Journal of Medicine*) looked at 3.6 million woman-years of OC use and found,

first, that stroke was quite rare in women on OCs—about 1 in 9,000 woman-years of use.⁵ And current use of an OC did not increase stroke risk (0.96 was the odds ratio). But in this study, fewer than 1% of women were using a 50-µg pill. That is more reflective of use in the United States today.

The discrepancy between US and international studies is probably best explained by the strong contraindication in the United States to using OCs in smokers over the age of 35. The majority of subjects in the WHO study were smokers.⁶ And the majority of strokes in that study involved 50-µg pills.

A recent pooled analysis of US studies showed no increased risk of stroke on OCs, but fewer than 1% of users were on high-dose pills, and only 17% of US OC users were smokers.⁷

In 2006, ACOG recommended against use of combined hormonal contraception in women with migraine with aura.⁸ This recommendation came before the introduction of 15- and even 10-µg OC formulations that inhibit ovulation. I have shown that inhibition of ovulation with these ultra-low-dose formulations decreased the frequency of aura in women with aura (as they were exposed to estrogen concentrations lower than those that occur in their own menstrual cycle).

I think it's time for ACOG's recommendations to be reassessed, given our current knowledge and current prescribing options.

JY: Could you briefly describe the concerns raised by ACOG regarding OC use for women with migraines?

Dr. Calhoun: Sure. First, there was a concern that all women with migraines are at increased risk of stroke if they take OCs. Although the 1975 *JAMA* article showed an increase of stroke risk with high-dose OCs, the risk in women with or without migraine was the same.⁴ In the WHO study, the authors themselves reported that risk went up with aura, with frequency of aura, and with number of years of migraine with aura, but there was no separate risk attributable to migraine.⁶

A pooled analysis of two US studies identified a statistically significant twofold increased risk of ischemic stroke among current users of OCs who reported migraine compared with women with migraines who did not use OCs.⁷ However, the "twofold increased risk of ischemic stroke" was based on only four cases. The actual raw prevalence of migraine was identical between cases and controls (4/51 cases and 14/182 controls). The relative risk of 2.08 was attained only after adjustment for other factors in four cases. The study's own authors urged caution in interpreting their data because "imprecise methods"—which differed between the two study sites—were used to assign the migraine diagnosis. Their final statement: "no firm conclusions can be drawn...."

A large Danish population-based case-control study found that among women with a history of migraine, the risk of stroke was elevated approximately threefold.⁹ That study is interesting for another reason: It showed that there was no increased risk of stroke with 20-µg OCs, but a fourfold increased risk with 5-µg OCs.

The threefold increased risk in migraineurs using OCs is suspect, as only 6% of controls were identified as migraineurs in

a population where 19% of women are reported to have migraine. An appropriate 17% of cases were identified as migraineurs.⁹ Did they selectively not allow migraineurs in the control group?

A very similar study in France found an equal distribution of migraine diagnosis between stroke cases and controls with a much more believable prevalence of migraine in the subjects.

JY: You mentioned the ACOG practice bulletin from 2006.⁸ That practice bulletin suggests that for women who have migraine with aura, regardless of their age, oral contraceptives should be avoided. And for women with migraine without aura over age 35, they should also be avoided. Do you agree with these recommendations?

Dr. Calhoun: I think the prohibition needs to be lifted, and we need to look at patients individually. This prohibition followed the World Health Organization collaborative study of cardiovascular disease and steroid hormone contraception.⁶ It was an international study with no US sites. They compared stroke cases with matched controls. The average age was over 35. Current OC use was found to be a risk factor for stroke; the odds ratio was 1.6. Other risk factors included hypertension (2.7); diabetes (2.8); family history of stroke (2.8).⁶

Now, if you add migraine as a separate risk factor, hypertension goes from 2.7 up to 3.3. Diabetes goes from 2.8 to 5.2 with migraine history added in. Family history of stroke goes from 2.8 to 3.4 with the additional risk factor of migraine. What happens if you add migraine to the risk factor of current OC use? Nothing. It goes from 1.6 to 1.6. So one of them—OC use or migraine—was not a separate risk factor.

The same authors who published the WHO study concluded that the adjusted risk of ischemic stroke was significantly associated with migraine of over 12 years' duration (4.5-times increased risk), migraine with aura (8-times increased risk), frequent migraine with aura, meaning over 12 times a year, (10-times increased risk). But, they said, in no case did correction for OC use alter these odds ratios. So, other factors were accounting for the increased risk of stroke.¹⁰

So I think we really need to go back and look at this issue.

The study that I mentioned before—the pooled analysis of two US studies, one done at Kaiser Permanente and the other at the University of Washington (this was the study that showed overall no increased risk of stroke with OCs, but there were four cases that, with some fancy statistics, supposedly doubled the risk with migraine).⁷ That study reflects how pills are prescribed in this country. Only 11 of the 1,564 cases and controls were using high-dose pills. Eleven of 1,500. But those 11 women accounted for four of the stroke cases. So, definitely higher risk with the high-dose pills. But more than 99% of US users were on high-dose pills. Only 1.6% of cases and controls were smokers using an OC. And the risk of stroke was only 11 per 100,000 woman-years.

So, I think the thing to look at here is who we're giving OCs to. Are we giving them to a smoker or a nonsmoker? Are we using a high-dose pill, or are we using an extremely low-dose product? Those are the nuances we need to consider, just as when we're prescribing for women with a host of other medical issues—weighing risks and benefits.

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