

Can Migraines be Effectively Managed with Combined Oral Contraceptives?

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Editorial

Women experience migraine headaches three times more often than men [1]. Migraine affects as many as 37% of reproductive-age women in the United States [2]. Migraines that occur during the menstrual cycles are resistant to treatment and lead to significant functional disability. Management of migraine in women has long been a clinical challenge.

A common belief about the cause of migraines in women is the fluctuation of the hormones estrogen and progesterone. In the normal menstrual cycle, estrogen rises rapidly during the first half, called the follicular phase, until mid-cycle where the levels dip prior to ovulation. Progesterone is only produced after ovulation. During the second half of the cycle, or luteal phase, the levels of both estrogen and progesterone fluctuate markedly. Estrogen rises again and progesterone increases until both peaks at day 23, which is 5 days prior to menstruation. If no fertilization occurs, the levels of estrogen and progesterone rapidly fall. The fall in the estrogen can trigger menstrual-related migraine headaches. Similarly, women who take combined estrogen and progesterone oral contraceptives (COCs) often experience migraines during the hormone-free interval. The fall in the estrogen caused by taking the placebo pills can trigger migraines. According to the International Classification of Headache Disorders (ICHD-II), the estrogen-withdrawal headache is defined as “a headache or migraine that develops within 5 days after cessation of estrogen use and resolves within 3 days.”

Migraines occur with or without an aura. Aura is usually a visual event occurring 5-60 minutes before the onset of headache. The visual aura is characterized by reversible symptoms such as a flickering uncolored zigzag line progressing laterally to the periphery of one visual field or laterally spreading scintillating scotomata. Several studies have associated a high risk of stroke in women who have migraines with aura [3,4]. The thought is that aura is associated with ischemic changes in the brain.

The underlying pathophysiology of migraine headaches is believed due to neurovascular dysfunction called cortical spreading depression. This phenomenon causes vasoconstriction, followed by rapid return to baseline vascular tone. Consequently, the process produces neuroinflammatory mediators that centrally sensitize and cause cutaneous allodynia, an exaggerated painful sensation due to a stimulus that does not normally provoke pain, and poor response to abortive treatment for migraine.

The first-line abortive treatments for migraines include non-steroidal anti-inflammatory drugs (NSAIDs) and triptans. NSAIDs function via several mechanisms including inhibiting the enzyme cyclooxygenase and prostaglandin synthesis, enhancing adrenergic transmission through increasing norepinephrine release, and suppressing inflammation. Triptans bind to 5-HT_{1B} and 5-HT_{1D} receptors in cranial blood vessels, causing vascular smooth muscle vasoconstriction and inhibiting vasoactive peptide synthesis.

Unfortunately, in treatment of chronic migraineurs where the number of headache days is greater than 15 per month, neither NSAIDs nor triptans are used as a preventative therapy because of the limitations of their side effect profiles. For those patients, non-hormone medications such as the antidepressants, antiepileptic drugs, beta-blockers, and calcium channel blockers are frequently administered but the responses are variable. For those women who suffer with chronic migraines and poorly respond to the non-hormone medication treatment, administration of COCs can effectively reduce the frequency of attacks by keeping their estrogen levels steady. This could be especially helpful for women suffering from menstrual-related migraines.

The administration of COCs has been proven effective in treating certain types of women migraineurs and is recommended in the practice guideline by the American Headache Association [5] and the American Congress of Obstetrics and Gynecology [6]. Several observational studies [7,8] and one prospective study [9] showed significant reductions in the number of headaches after changing from a standard regimen (21/7 day) to an extended regimen of COCs, suggesting that sustained levels of estrogen can prevent this subset of headaches. A recent comprehensive review by Edlow and Bartz [2] outlined this regard.

In a World Health Organization (WHO) Collaborative study concerning cardiovascular diseases and steroid hormone contraception, the adjusted risk of ischemic stroke was significantly correlated with migraine with aura, while there was no significant increase in women who experienced migraine without aura [10]. Similarly, a prospective study found a significant increase in strokes among migraineurs with aura, though the absolute risk was low 3.8 cases per 10,000 [4]. The additional risk of ischemic stroke attributable to women with migraines using COCs has been estimated as 8 per 100,000 women at age 20 years, and 80 per 100,000 women at age 40 years [11]. However, level 2 evidence from an US population-based case-control study of women with migraines who use COCs, showed a pooled-odds ratio of 2.08 (95% CI, 1.19 to 3.65) for ischemic stroke [12]. A large Danish population-based case-control study found that among women with a history of migraine headaches, there was a threefold increase in the risk of stroke ($p < 0.01$) [13]. Neither of the studies differentiated between migraine with and without aura.

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Importantly, COCs are not suitable for all women with migraines. Because of the possibility of increased risk for ischemic stroke, it is recommended that the administration of COCs should be avoided in women migraineurs with aura, over 35 years, history of clotting disorder such as deep venous thrombosis, family history of heart attack or stroke under age 60 years, cardiovascular risk factors such as high blood pressure, high cholesterol, low HDL cholesterol, obesity, smoking and high-sensitivity C-reactive protein [14-16].

When prescribed within established guidelines, COCs could maximally benefit women with menstrual-related migraines and the estrogen effect may not impact on stroke risk.

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