

Headache and Combination Estrogen-Progestin Oral Contraceptives: Integrating Evidence, Guidelines, and Clinical Practice

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Primary headache disorders such as migraine affect almost a third of women during their childbearing years, when decisions about contraception must be made. Headache is also a commonly reported adverse event in clinical trials of oral contraceptives (OCs). Health care practitioners will frequently be called upon to give advice about the use of OCs to women with headache. This article applies current evidence, guidelines, and recommendations about headache and OC use to treatment decisions in four clinical scenarios: initiating OC use in a woman who has migraine without aura, continuing OC use in a woman who experiences worsening of migraine and the development of aura after initiating OCs, initiating OC use in a woman with tension-type headache (TTH) and a family history of migraine, and use of an extended duration OC regimen to minimize migraine triggered by estrogen withdrawal. The authors' recommendations regarding OC use in various primary headache disorders are summarized.

Key words: oral contraceptives, migraine, review, guidelines, recommendations

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Decisions to initiate or continue oral contraceptives (OCs) are influenced by both safety risks and nondangerous "nuisance" side effects. Headache is a side effect that is frequently mentioned as a reason not to begin or continue use of OCs.^{1,2} Because the background prevalence of headache is high in the population of women most likely to use OCs, it can be difficult to evaluate headache associated with OC use.

Combination OCs (COCs) are used by over 100 million women. Most OCs in use today contain between 20 and 50 (μg) of ethinyl estradiol and a progestin.³ Traditional 28-day combination regimens consist of active pills administered for 21 days, followed by 7 days of no tablets or placebo tablets. The doses

of estrogen and progesterone can remain the same (monophasic) or vary (biphasic or triphasic). Doses of estrogen in OCs have decreased steadily over the years because lower doses of estrogen reduce the risk of thrombotic complications and do not decrease contraceptive efficacy.³

In addition to being the most effective form of contraception, it is well established that OCs provide noncontraceptive benefits, including lowered risks of ovarian carcinoma, endometrial carcinoma, acute pelvic inflammatory disease, fibrocystic disease of the breast, ovarian cysts, ectopic pregnancy, menstrual disorders, and anemia. Several OC risks are also well established, especially stroke, venous thromboembolism, and cerebral venous thrombosis.³ Recently analyzed results from the Women's Health Initiative provide strong evidence that OC use decreases the risk of heart attack and high cholesterol.⁴ Current or former OC use does not appear to raise the risk of breast cancer.⁵

Because both OC use and headache are common, physicians will frequently be asked to provide advice to women about their interaction. This article

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applies current evidence about headache and OC use to treatment decisions in four clinical scenarios: initiating OC use in a woman who has migraine without aura; continuing OC use in a woman who experiences worsening of migraine with aura; initiating OC use in a woman with tension-type headache (TTH); and use of an extended duration OC regimen to treat migraine triggered by estrogen withdrawal.

CASE 1

A 23-year-old woman has severe dysmenorrhea that has been unresponsive to treatment with NSAIDs. She has migraine without aura and takes sodium valproate 250 mg twice daily for migraine prevention. Because she desires contraception, OCs have been recommended as treatment of dysmenorrhea. The patient has heard through friends and the popular press that because she has migraine she should not use OCs. Her neurologic examination is normal and she has no other contraindications to OC use.

Background.—Migraine affects up to 28% of women during their childbearing years, when decisions about contraception must be made.⁶ OCs are effective treatment for dysmenorrhea. Some experts believe their use in women with endometriosis, a possible cause of dysmenorrhea in this patient, may preserve fertility.⁷ In deciding whether OC use is appropriate in a woman with migraine, safety issues must be distinguished from tolerability issues.

Evidence and Guidelines.—*Safety.*—Migraine and OC use are both risk factors for ischemic stroke. The risk of stroke in childbearing age women is low, but good quality evidence suggests that a diagnosis of migraine without aura increases this risk by a factor of about 3. The combination of migraine and OC use increases the risk of stroke by a factor of about 14.⁸⁻¹⁰ Stroke risk appears to be higher with OCs containing high doses of estrogen (greater than 50 μg of ethinyl estradiol). Interestingly, migraine appears to be a risk factor for stroke only in women under the age of 45.

Tolerability.—OCs are widely believed to cause or aggravate headache, but the evidence that this is a common or clinically significant problem is remarkably slim. The authors recently completed a systematic review of the medical literature aimed at assessing that headache can be caused by OC use. Analysis of clinical

trials including an active, untreated or placebo control group of women for comparison showed only small increases in headache activity early in treatment. Regardless of cause, headache occurring in association with OC use tended to improve despite continued OC use.¹¹

Migraine in women using traditional COCs is more likely to occur during the pill-free week, presumably triggered by estrogen withdrawal. The magnitude of the drop in estrogen may also influence the likelihood that headache will occur. OCs containing lower levels of estrogen may be less likely to provoke headache. Paradoxically, however, very low estrogen OCs (those containing 20 or 25 μg of ethinyl estradiol) may not completely suppress ovarian function or endogenous estrogen production.¹² This may explain why no improvement in headache was observed in two trials that switched patients to low-dose OCs.^{13,14} Very low-dose OCs are also associated with high levels of patient dissatisfaction due to breakthrough bleeding.¹⁵ There is no evidence that the dose or type of progestin in an OC has an important influence on headache.¹¹

Guidelines.—Consensus-based guidelines and recommendations regarding the use of OCs in women with various medical conditions have been issued by several professional organizations.¹⁶⁻¹⁸ All discourage the use of OCs in some women with migraine. In general, World Health Organization (WHO) and American College of Obstetrics and Gynecology (ACOG) guidelines consider that for women under the age of 35 who have migraine without aura, and few or no cardiovascular risk factors, the benefits of OC use typically outweigh the risks (see Table 1).

The International Headache Society task force on combined OCs and hormone replacement therapy in women with migraine concluded that “there is no contraindication to the use of COCs in women with migraine in the absence of migraine aura or other risk factors.”¹⁸

Recommendations.—This patient has migraine without aura, is under 35, has no additional risk factors for stroke, and is likely to experience important improvement in another condition from OC use. Avoidance of unintended pregnancy is especially important in this patient because she is taking valproate, a known teratogen.¹⁹ For her, the benefits of OC use probably

Table 1.—American College of Obstetricians and Gynecologist (ACOG) and World Health Organization (WHO) Guidelines for the Use of Combination Estrogen-Progestin Oral Contraceptives in Women With Migraine*

Variable	ACOG Guidelines (14)	WHO Guidelines (15)
Age \geq 35 years	Risk usually outweighs benefits	Risk usually outweighs benefits
Focal symptoms	Risk unacceptable	Risk unacceptable

ACOG guidelines recommend the use of the formulation containing less than 50 μ g of ethinyl estradiol with the “lowest progestin dose.” WHO guidelines recommend the use of formulations containing 35 μ g or less of ethinyl estradiol and do not mention the dose or type of progestin.

outweigh the drawbacks, and this assessment is supported by professional guidelines. A monophasic OC containing 35 μ g of ethinyl estradiol would probably provide the best balance between safety and tolerability.

It would be wise to obtain a baseline assessment of the frequency, severity, and character of this patient’s headaches and then monitor their frequency and severity while she is using OCs. Use should be reassessed if headaches worsen in frequency or severity or neurologic accompaniments develop (eg, aura). If a method of birth control less effective than OCs is chosen, replacement of the valproate with an alternative migraine prophylactic agent that is not associated with serious birth defects should be considered. Characterizing the cause of this patient’s dysmenorrhea would be helpful in narrowing the harm to benefit equation.

CASE 2

A 38-year-old woman consults a new physician 6 months after beginning COC use. Shortly after starting OCs, she began to experience headaches twice a week lasting 12 to 16 hours. The headaches are bilateral, throbbing, and accompanied by nausea and sensitivity to light and sound. They are preceded by a 45-minute visual disturbance consisting of a “bright, shimmering, zigzag line” that enlarges, moves to the periphery of her visual field and then fades away as the headache begins. Upon questioning, she reports occasional sim-

ilar headaches prior to OC use that were “not as bad.” The visual disturbance associated with the headache is new. Her neurologic examination is normal. The patient smokes 1 pack per day of cigarettes.

Background.—The prescribing information for combination estrogen-progestin OCs typically lists “migraine with focal neurologic symptoms” as a contraindication to the use of OCs and states that “the onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of OCs and evaluation of the cause.”²⁰

Evidence and Guidelines.—*Safety.*—Migraine with aura is a statistically independent risk factor for ischemic stroke, as is OC use. The risk of stroke in women who have migraine with aura is increased by a factor of about 6 to 8, and further increased in the presence of other risk factors. Women with migraine who smoke 1 or more packs of cigarettes per day raise their risk by a factor of about 10. If they also use OCs, the odds ratio for stroke is elevated to 34.^{8-10,21}

Tolerability.—There is some evidence that the risk of headache worsening or onset is greater in women who have migraine with aura compared with those who have migraine without aura, with an odds ratio of around 4.²² There have been suggestions that exogenous estrogen may precipitate aura or cause it to increase in frequency. Evidence also suggests that the risk of developing headache with OC use is higher in patients over 35 years of age.^{23,24}

Guidelines.—Because of concerns about the interaction of two risk factors for stroke (OC use and migraine with aura), WHO and ACOG guidelines recommend that women who experience migraine with focal neurological symptoms not use OCs (see Table 1). These guidelines also suggest that the risks of OC use are “unacceptable” or “outweigh the benefits” if a woman is a smoker, over the age of 35, has uncontrolled hypertension, a history of stroke, or has had breast cancer within the past 5 years. It is not entirely clear why WHO and ACOG guidelines view age 35 as a threshold beyond which OC use is unacceptable. In the case of stroke risk attributable to migraine, it is actually women *under* 45 whose stroke risk is elevated. There is no evidence that migraine is a risk factor for ischemic stroke in women over 45.⁹

Table 2.—International Headache Society Task Force Recommendations on Combined Oral Contraceptive Use in Women With Migraine³⁴

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1. Identify and evaluate risk factors.
 2. Diagnose migraine type, particularly the presence of aura.
 3. Women with migraine who smoke should stop smoking before starting COCs.
 4. Other risk factors, such as hypertension and hyperlipidaemia, should be treated.
 5. Consider nonethinylestradiol methods in women who are at increased risk of ischemic stroke, particularly those who have multiple risk factors. Some of these contraceptives are as or more effective in preventing pregnancy than COCs and include progestogen-only hormonal contraception. Observational studies suggest that progestogen-only hormonal contraceptive use is not associated with an increased risk of ischemic stroke, although quantifiable data are limited.
- Migraine-related symptoms that may necessitate further evaluation and/or cessation of COCs
1. New persisting headache.
 2. New onset of migraine aura.
 3. Increased headache frequency or intensity.
 4. Development of unusual aura symptoms, particularly prolonged aura.
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A task force convened by the International Headache Society to assess the use of OCs in women with migraine concluded that “there is a potentially increased risk of ischemic stroke in women with migraine who are using COCs and have additional risk factors which cannot easily be controlled, including migraine with aura. One must individually assess and evaluate these risks. Combined oral contraceptive use may be contraindicated” (Table 2). The task force also concluded that “an increase in attack frequency or severity with OCs is itself an indication for stopping OC, whether or not it is associated with an increased risk of stroke. A change in the character of attacks after starting OC use is possibly of greater concern, but the evidence is conflicting. The thresholds of migraine severity and frequency that represent the contraindication or discontinuation of OCs are still to be determined, and are different for migraine with and without aura Migraineurs who smoke heavily or have multiple thrombotic risk factors should be advised not to take COCs. When patients with migraine are placed on COCs they should be carefully monitored. If migraines worsen or if there is new-onset migraine related to OC use, one should take into account the patient’s age, the type of migraine, the frequency and severity of attacks, and the presence of other vascular risk factors. . . . One must be more restrictive in women with migraine with aura, in smokers, and in older women, as the risk of stroke is higher in these individuals. Any unusual headache that has a sudden onset, a long duration, or is associated with focal neurologic symptoms that differ from typical aura should prompt the immediate

discontinuation of OCs, and appropriate neurologic investigations to rule out a cerebrovascular complication should be considered.”¹⁸

Recommendations.—This patient has a history of occasional migraine without aura that was not recognized prior to beginning OC use. Migraine without aura by itself is not a contraindication to OC use, but this patient has additional stroke risk factors of age and smoking. Coincident with OC use, her headaches have increased in frequency and are now associated with neurologic accompaniments that meet diagnostic criteria for aura. In general, a worsening of headaches, either in severity or frequency, or the new onset of headaches or neurologic accompaniments to headache requires further evaluation.

For this patient, it would be prudent to use other forms of birth control. A progestin-only pill, subdermal implants, or injectable contraception could also be used. However, this decision must be weighed with care if the patient has factors that might predispose her to a high-risk pregnancy should she use a less-effective contraceptive method and conceive. The patient should be encouraged and assisted to discontinue smoking. If headaches do not improve promptly following OC discontinuation, this patient should be referred to a neurologist or headache specialist for treatment.

CASE 3

A 20-year-old woman would like to begin OC use, but has an older sister whose severe migraine headaches began when she started OC use. A maternal

grandmother had frequent “sick headaches.” The patient reports a personal history of mild headaches occurring 6 to 8 times yearly for the past 4 years. These last 3 to 4 hours and are bilateral, pressing, or tightening in quality, and not associated with nausea, vomiting, photophobia, or phonophobia. The headaches respond well to over-the-counter medications such as NSAIDs. Her neurologic examination is normal and there are no other contraindications to OC use.

Background.—The lifetime prevalence of episodic tension-type headache (TTH) approaches 90%.²⁵ TTH is usually self-managed and leads to medical consultation only when it becomes frequent. Studies have shown that a diagnosis of TTH assigned in primary care settings is frequently inaccurate, however, primarily because a diagnosis of migraine has been missed.²⁶ TTH frequently coexists with migraine. Genetic factors play an important role in the development of migraine, and patients with a strong family history but no personal history of migraine may be at increased risk of developing migraine in the face of environmental triggers.

Evidence and Guidelines.—*Safety.*—There is no evidence that TTH is a risk factor for the development of ischemic stroke.

Tolerability.—There is no evidence that hormonal fluctuations play a role in the pathogenesis or clinical course of TTH. There is modest evidence that a family history of migraine increases the risk of developing headache on OCs.²³

Guidelines.—TTH is not considered a contraindication to OC use by any professional guidelines.

Recommendations.—Diagnoses of TTH are frequently inaccurate.²⁶ Thus, it is important to ascertain through careful questioning that the patient does in fact have TTH and not migraine, which is sometimes a contraindication to OC use. This patient’s headaches do meet diagnostic criteria for episodic TTH. While the presence of TTH does not contraindicate OC use in this patient, the strong family history of migraine does increase the risk that she will develop new-onset migraine with OC use.²³ Because she is in an age group where the background incidence of migraine is high, it would be difficult to determine whether worsening headache with OC use was causal or coincidental.

The decision about OC use in this case must be made by the patient and her health care provider. It

involves weighing the potential benefits of OC use and the strength of other reasons for OC use against the small but real risk of headache precipitation. The patient may have compelling reasons for OC use that she judges outweigh the risk of headache. Conversely, if her sister has severe, disabling headaches that have been unresponsive to treatment, the prospect of developing headache might be unacceptable to her.

CASE 4

A 33-year-old woman has used COCs since college and is generally satisfied with them. She has an average of 13 episodes of migraine without aura yearly that occur almost exclusively during the pill-free week of her OC regimen. She seeks advice about reports in the popular press suggesting that extended duration OC use may decrease estrogen-withdrawal symptoms such as headache. She has no other contraindications to OC use and her neurologic exam is normal.

Background.—Headache is consistently among the top two or three symptoms reported during the pill-free week.²⁷ As early as the 1960s, Whitty noted that women who used OCs continuously (without the pill-free week) had fewer headaches.²⁸ Extended duration or continuous OC use is increasing in popularity. Such regimens generally involve administration of active, hormone-containing pills for extended periods of time with shorter or less frequent period of placebo or inactive pills. Reasons for the use of extended duration OC regimens include convenience, patient desire for fewer episodes of withdrawal bleeding, and a desire to minimize the occurrence of headache and other estrogen-withdrawal symptoms.²⁹ The United States Food and Drug Administration recently approved a 91-day OC regimen in which active tablets are taken for 84 consecutive days, followed by 7 days of inactive tablets. Women using this product experience four bleeding episodes per year, in contrast to the 12 to 13 episodes that would occur with traditional COC use.³⁰

Evidence and Guidelines.—*Safety.*—Extended duration OC regimens modestly increase overall patient exposure to hormones, by reducing the number of days on which no active pills are taken. The long-term health effects of this slight increase in hormone exposure are unknown, but probably minimal.

Tolerability.—Several studies have assessed the tolerability of extended duration OC regimens. In

particular, common estrogen-withdrawal symptoms, including headache, appear to be less frequent.^{29,31,32} Studies using other methods to minimize estrogen withdrawal during the pill-free week of traditional OC use provide indirect evidence that extended duration dosing should decrease the risk of headache during that time. A recent pilot study of 14 women with migraine who used 50 μg estrogen patches during the pill-free interval of a traditional contraceptive regimen showed a reduction in the frequency and severity of migraine at that time.³³

Guidelines.—Existing guidelines regarding the use of OCs in women with migraine apply to traditional 28-day combination estrogen-progestin OC regimens. American College of Obstetrics (Gynecology guidelines and International Headache Society recommendations endorse the use of formulations containing less than 50 μg of ethinyl estradiol, while the World Health Organization guidelines recommend the use of OCs containing 35 μg or less of ethinyl estradiol.¹⁶⁻¹⁸ No professional guidelines or recommendations address continuous or extended duration use of OCs.

Recommendations.—Hormonal manipulation is not the first-line treatment for estrogen-withdrawal headaches. However, this patient is already using OCs for contraceptive purposes and would like to have fewer episodes of withdrawal bleeding. She has no

other contraindications to OC use. With the exception of headache during the placebo week, she has tolerated OCs well for more than a decade. Thus, a trial of extended duration OC use, in an attempt to minimize headache, is reasonable. This patient should be counseled about the unknown, but probably small, risks associated with a slight overall increase in hormonal exposure with this method. Additionally, she should be closely monitored in order to ascertain any headache changes on this treatment.

CONCLUSIONS

The authors' recommendations regarding the use of OCs in women with selected primary headache disorders are summarized in Table 3. Migraine without aura is not a contraindication to OC use in the absence of other risk factors for stroke, and the likelihood that migraine will worsen with use is low. In addition, headaches that emerge during the early months of OC use often improve despite continued OC use. Extended duration OC regimens may be helpful for women who experience headache during the pill-free week of traditional COC use.

OC use should be reconsidered if patients develop significant worsening of headache or develop neurologic accompaniments to headache. Decisions about OC use in patients who have migraine with

Table 3.—Recommendations Regarding OC Use in Selected Primary Headache Disorders

Tension-type headache

- Not a contraindication to OC use

Migraine without aura

- Not a contraindication to OC use in patients under 35 or without additional stroke risk factors
- Clinical judgment should be used in deciding whether advantages of OC use may outweigh risks in selected patients over 35 or with other stroke risk factors
- Monitor frequency and severity of headaches during use of OCs
- Reassess use if headaches worsen or neurologic accompaniments develop (e.g., aura)

Migraine with aura

- Consider alternative forms of birth control
- Recognize that there is a spectrum of aura severity, ranging from prolonged, dramatic auras with every headache to aura experienced only once or twice during a lifetime. Common sense and expert opinion suggests that the stroke risk may vary accordingly; definitive evidence on this point is lacking and clinical judgment should be used.

Cluster headache

- Insufficient evidence for any recommendations regarding OC use in this rare headache syndrome that is more common in men

Women with no personal but a strong family history of headache or migraine

- Modest evidence of increased risk of headache precipitation with OC use, especially if over the age of 35; monitor closely if OCs are used
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aura must be individualized. Consensus-based professional guidelines recommend against OC use for most women who have migraine with aura, but the variable spectrum of aura severity makes such blanket recommendations difficult to apply in clinical practice. TTH is not a contraindication to OC use and does not require discontinuation of OCs if it develops in a current user. There is insufficient evidence to make any recommendations about the use of OCs in women who have cluster headache. The risk of developing headache with OC use may be increased in older women or those with a strong family history of troublesome headaches.

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