REVIEW ARTICLE

Migraine and Oral Contraceptives

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ABSTRACT: Initiation of oral contraceptive (OC) therapy in migraine may worsen pre-existing migraine or change the pattern of the individual migraine attacks. Many women experience no change in their migraine and a few show improvement. Evidence is accumulating that migraine increases ischemic stroke risk and that this risk is higher in migraine with aura than in migraine without aura. OCs also increase stroke risk, and the increased stroke risk attributable to each of migraine and OC therapy may be additive. The risk of ischemic stroke in young women is very low and likely remains acceptably low in young women with migraine without aura and in those with a simple migraine aura when OCs are prescribed. However, the presence of a complex or prolonged migraine aura, or of additional stroke risk factors such as increased age, smoking, and hypertension likely increases the ischemic stroke risk further in patients with migraine when OCs are prescribed. Whether OCs can be prescribed safely for the patient with migraine depends upon many factors including patient age, type of migraine, and the presence or absence of other stroke risk factors.

RÉSUMÉ: Migraine et contraceptifs oraux. La prise de contraceptifs oraux peut aggraver les symptômes chez une migraineuse ou modifier le tableau clinique lors des crises. Plusieurs femmes ne présentent pas de changement de leur symptomatologie migraineuse et un petit nombre note une amélioration. Il y a de plus en plus d'évidence que la migraine augmente le risque d'accident vasculaire cérébral ischémique et que ce risque est plus élevé dans la migraine avec aura que dans la migraine sans aura. Les contraceptifs oraux augmentent également le risque d'accident vasculaire cérébral et les risques accrus d'accident vasculaire cérébral attribuable à chacun pourraient être additifs. Le risque d'un accident vasculaire cérébral ischémique chez une femme jeune est très faible et demeurera probablement à un niveau acceptable chez les jeunes femmes migraineuses sans aura et chez celles qui ont une aura simple quand les contraceptifs oraux sont prescrits. Cependant, la présence de migraine avec aura complexe ou prolongée ou de facteurs de risque additionnels d'accident vasculaire cérébral tels que l'âge, le tabagisme et l'hypertension augmente vraisemblablement davantage le risque d'accident vasculaire cérébral ischémique chez les migraineuses quand on prescrit des contraceptifs oraux. La sécurité de la prescription de contraceptifs oraux chez les patientes migraineuses dépend de plusieurs facteurs incluant l'âge de la patiente, le type de migraine et la présence ou l'absence d'autres facteurs de risque d'accident vasculaire cérébral.

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Migraine headache is most frequent in young women, and this is the very population that uses oral contraceptives (OC). Two major issues therefore arise:

1. What is the effect of OC use on the frequency and severity of migraine headache attacks?

2. Do OCs pose any unusual risk (over and above that which may exist for the general population) for the migraine patient in terms of stroke?

The whole issue of migraine and OC use is controversial for several reasons. Firstly, many of the pertinent studies have methodological flaws. Secondly, the dosage of the estrogens and progestins contained in OCs have progressively decreased over time, so that the results of some of the older studies may no longer be applicable today. Thirdly, there are several different types of migraine, for example migraine without aura and migraine with aura. Some migraine patients have prolonged auras, or additional features which might place them at increased risk for stroke. Statistics which might therefore apply to the migraine population as a whole do not necessarily apply to any given subgroup of migraine sufferers.

Effects of Oral Contraceptive Use on Migraine Attacks

As long ago as 1975, Bickerstaff[1] stated that, from the accumulated evidence, four main effects upon migraine sufferers who started the pill had emerged: 1) The migraine attacks may start for the first time; 2) Existing migraine may become worse or increasingly frequent; 3) The pattern of symptoms in the individual's existing attacks may be altered; 4) Paradoxically, in some patients there may be a distinct improvement.

To these four options, a fifth one must be added: 5) In the majority of migrainous women, the pattern of migraine does not change when they go on OCs.

Bickerstaff pointed out that some women experienced migraine attacks for the first time within days or weeks of starting

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the pill, and these would stop when the pill was stopped. Other investigators have noted the same phenomenon. In one study, onset of migraine during OC use was observed ten times more frequently than in a control group of women who were not using OCs.[2] Furthermore, although new onset migraine usually occurs in the early cycles of pill usage, it can also occur after prolonged usage.[3] OC related new onset migraine has been said to occur more frequently in women with a family history of migraine, although one study found that these patients had a positive family history less frequently than those who had migraine before oral contraceptive use.[4] To complicate matters, although stopping OCs usually results in immediate relief of OC-induced migraine, there may be a delay of up to a year.[4] Pill use is highest in young women and this is also the age group in which migraine frequently develops spontaneously. This makes it more difficult to ascertain cause and effect.

Bickerstaff stressed the possibility of accentuation of pre-existing migraine, and indicated that this is the effect most commonly encountered. As described by him, shortly after starting the pill, these women find their attacks increase three or fourfold in number and are of considerably greater severity. This increase is reversed when the pill is discontinued. Various studies report an increase in the frequency or severity of attacks in 18-50% of migraineurs who take the pill.[5,6]

The third option, a change in the pattern of the individual migraine attacks, was in Bickerstaff's opinion the most important facet of the whole problem revolving around the pill and migraine, although he did not consider it common. He singled out patients with a long history of migraine without aura who suddenly developed migraine with aura after going on the pill, or even aura without following headache. Although he felt that the majority of these patients came to no harm, he considered immediate cessation of the pill was mandatory as these patients might be at increased risk for stroke. That these patients might be at a significantly increased risk for migrainous infarction, has also been indicated by others[7] based on small series of patients without controls. Gardner, again based on a small series of patients, attempted to define a syndrome of increasing headache, often with focal neurological symptoms, which seemed to occur in some patients with migraine on the pill prior to cerebral infarction.[8]

Bickerstaff considered the fourth group, those whose headaches improved on the pill, to be something of a paradox. These were typically women subject to migraine whose attacks had a distinct menstrual relationship. While on the pill, they had marked relief, although remaining attacks still tended to occur during the week off the pill. He felt, however, that it was rarely useful to attempt to treat migraine by prescribing OCs, and that these beneficial responses to the pill were unusual and usually discovered by accident. Others have also noted improvement in some patients with migraine when the pill is started, and have indicated that this may occur in up to 35% of patients.[2] Some authors have suggested that a trial of oral contraceptives may be indicated in women with intractable menstrual migraine, particularly if associated with severe dysmenorrhea.[9] If such therapy is attempted however, these patients must be followed closely for headache aggravation or the development of neurological symptoms.

In the majority of women with migraine who go on the pill, it would appear that the pattern of migraine simply does not change significantly.[3] Some placebo controlled studies have shown no difference in headache when women take some estrogen-containing oral contraceptives,[10] but the power of these studies may not have been sufficient to detect smaller differences. It may be that this fifth option of no change in the patient's headache may be becoming more common because of the current use of lower dose estrogen and progestin contraceptives.

Migraine, Oral Contraceptives and Stroke Risk

There are three issues which must be considered when discussing oral contraceptive use and stroke risk in patients with migraine: 1) Does migraine itself increase stroke risk? 2) Do OCs increase stroke risk in women without migraine? 3) If migraine increases stroke risk, do OCs cause additional stroke risk in women with migraine?

Does Migraine Itself Increase Stroke Risk? There are several reasons why cerebral infarction might be more common in patients with migraine. Firstly, it is possible that the vasoconstriction associated with the migraine aura might be severe enough to at times result in cerebral infarction, or at least contribute to a critical reduction in cerebral perfusion in association with other factors. Secondly, the severe nausea and vomiting which some migraine sufferers experience with their migraine attacks could lead to dehydration, which in turn could predispose to cerebral vascular thrombosis, especially cerebral venous thrombosis. Thirdly, platelet activation occurs during acute migraine attacks,[11] and this might predispose to vascular occlusion. There may also be some increase in platelet activity between attacks.[12]

Several different mechanisms might cause ischemic stroke in migraine sufferers. Cerebral infarction might result from the usual causes of embolism and thrombosis. On the other hand, the International Headache Society (IHS) classification[13] recognizes that the pathophysiology of the migraine attack itself might lead to cerebral infarction. This entity is termed migrainous infarction (category 1.6.2). To meet the criteria for migrainous infarction, the patient must have a history of migraine with aura and the migraine attack leading to stroke must be typical of previous attacks. To diagnose migrainous infarction, the neurological deficit produced by the aura must still be present to some extent, seven days later, or infarction must be demonstrated in the relevant area by neuroimaging. In addition, other causes of infarction must be ruled out by appropriate investigations.

Because this review focuses on the use of oral contraceptives in patients with migraine, this section will focus on epidemiologic studies which addressed stroke risk in female migraineurs under the age of 45. As can be seen from Table 1, there is strong evidence that migraine headache sufferers have a greater risk of experiencing ischemic stroke as compared to non-migraineurs. The case control studies shown in Table 1 all had a similar design, in that the prevalence of migraine was established for a group of young women with ischemic stroke, and this prevalence was then compared to the prevalence of migraine in a matched control group. The Collaborative Group Study[14] found the weakest association between migraine and stroke, but also used the least clearcut definition of migraine. For its purposes, women reporting two or more characteristic symptoms of migraine (such as unilateral headache, throbbing quality of pain, etc.) were considered to have migraine. The studies by Tzourio

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et al.[15,16] used the IHS diagnostic criteria for migraine, and as a result likely provide stronger evidence for an association between migraine and ischemic stroke. Table 1 indicates that the ischemic stroke risk for patients with migraine with aura is considerably higher than that for patients who suffer only from migraine without aura. The Collaborative Stroke Study also provided some evidence that patients with migraine were at increased risk of hemorrhagic stroke, although this evidence was not as strong as that for ischemic stroke.

Table 1: Occurrence of Migraine in Young Women (< age 45) with Ischemic Stroke, Compared to Controls (odds ratios).

STUDY	Any Migraine Type	Migraine without Aura	Migraine with Aura
Collaborative Group 1975[14]	2.0* (1.2-3.3)**		
Tzourio et al. 1993+ [15]	4.3 (1.2-16.3)		
Tzourio et al. 1995++ [16]	3.5 (1.8-6.4)	3.0 (1.5-5.8)	6.2 (2.1-18.0)

* Using neighbour controls ($p<0.05$). Hospital controls resulted in a non-significant odds ratio of 1.2.

** 95% confidence intervals

\+ $p = 0.03$

++ $p<0.001$ for all migraine types. Adjusted odds ratios are shown, controlling for age, tobacco smoking, history of hypertension, and use of oral contraceptives.

What types of ischemic strokes occurred in the patients with migraine? The Collaborative Group Study does not elaborate upon stroke types observed, or their timing in relation to the migraine headache attacks. Tzourio et al.[16] in their 1995 study indicate that none of their patients met the IHS criteria for migrainous infarction. Ten strokes in their series occurred in women with migraine with aura, and of these, five strokes occurred in association with a headache attack. However, the neurologic deficits in these patients were different from those experienced during their aura. It would appear that the majority of ischemic strokes in migraine patients result from the usual factors including thrombosis and embolism, but more information is needed. Tzourio et al.[16] indicate that the prevalence of migraine in their study was similar in patients with stroke with demonstrated arterial lesions, cardiac abnormalities, and systemic disorders. Of interest, in their 72 stroke patients (of whom 60% had migraine), they found 22 arterial dissections and six patients with anticardiolipin antibodies. They make no mention of mitral valve prolapse, even though 88% of their patients underwent echocardiography.

In conclusion, patients with migraine appear to have an increased risk of ischemic stroke, and this risk is higher in patients who have migraine with aura.

Do OCs Increase Stroke Risk in Women Without Migraine? There are several reasons why OCs might increase stroke risk. Firstly, many of the progestins used in OCs have intrinsic androgenicity, affect lipid and lipoprotein metabolism, and therefore might have atherogenic potential.[17] Secondly, at least the older high dose OCs caused increased glucose levels after glucose challenge and marked elevations in insulin.[18] They therefore had significant effects on carbohydrate metabolism. Thirdly, combination OCs may affect blood coagulation, and it is usually considered that the thromboembolic morbidity of the OCs is related primarily to the estrogen component.[17] The situation however is undoubtedly much more complex, and effects on various other factors, including the fibrinolytic system, are not ruled out.

Several very large studies have addressed the issue of whether oral contraceptives increase stroke risk. Unfortunately, the results of many of these are likely no longer fully applicable. Since the OCs were first introduced in North America more than 30 years ago, both the estrogen and progestin dosage components have decreased by threefold to fourfold. Associated with this reduction in dosage, there has been a reduction in the risk of thromboembolism and coronary heart disease. The metabolic effects of the OCs such as those affecting lipids and coagulation factors have also been reduced.[19] Meade et al. found that deaths and ischemic heart disease were reported significantly less frequently for patients taking OCs containing 30 micrograms of estrogen, as compared to those taking preparations containing 50 micrograms.[20] In a literature review, Stadel[21] concluded that there appeared to be a direct relation between the estrogen content of oral contraceptives and the risk of overt venous thromboembolic disease. OCs containing 50 to 80 micrograms of estrogen seemed to be only one-third to one-half as likely to precipitate fatal or non-fatal pulmonary embolism as OCs containing 100 to 150 micrograms of estrogen. Whether a similar risk reduction in stroke incidence occurs is less clear, but there seems little doubt that some risk reduction does occur with the use of lower dose estrogen preparations. Tzourio et al.[16] does provide evidence that ischemic stroke risk falls as the estrogen dose in OCs decreases from 50 μg to 20 μg.

The older epidemiological studies do raise cause for concern. The Collaborative Group for the Study of Stroke in Young Women showed that the relative risk of thrombotic stroke for all women using oral contraceptives was approximately four (4.1 for neighbour controls, 4.4 for hospital controls) as compared to women not using oral contraceptives.[14] The Royal College of General Practitioners' oral contraception study[22] found that women who had used the pill had a relative risk of 4.3 for deaths attributed to vascular diseases, with most deaths being from ischemic heart disease and subarachnoid hemorrhage. This relative risk appeared to apply primarily to women over age 35, and was highest in smokers. This study concluded that for women 45 years of age and above, the use of OCs could be justified only in exceptional circumstances.

Notwithstanding the above, it would appear that the newer low dose OCs, when prescribed for healthy women, are extremely safe. Porter et al.[23] found not a single case of stroke or myocardial infarction in 30,000 person-years of OC use by women who were otherwise healthy, i.e., did not have risk factors for stroke such as treated hypertension, diabetes, recent surgery, recent pregnancy, etc. In summary, current OCs containing 30 micrograms of estrogen and the newer progestins such as desogesterel which have very little intrinsic androgenicity would appear to be extremely safe, particularly in women without significant cardiovascular risk factors.

Do OCs Increase Stroke Risk in Women with Migraine? There is evidence that the increased risks of stroke attributable

to each of migraine and OCs may be additive. The data shown in Table 2 are extracted from the two case control studies which address this issue. As can be seen, in the Collaborative Stroke Study,[14] the relative stroke risk for migraine patients who took the pill was 5.9, compared to women without migraine who did not use OCs. In Tzourio et al.,[16] the corresponding figure was a relative risk of 13.9. In such sub-group analyses, however, the number of patients with stroke on which these figures are based become quite small for both studies, and the 95% confidence intervals are wide. In fact, the results of the Collaborative Group Study are within the confidence intervals of the Tzourio study. These studies do raise the possibility, however, that if OC use increases stroke risk in non-migraineurs by a factor of approximately 3.5,[16] it may increase the stroke risk in migraine sufferers by a similar factor. In that case, the stroke risk for some migraine sufferers using OCs becomes substantial, and might be quite substantial depending upon the woman's age and whether or not she has migraine with aura.

Table 2: Relative Risk of Ischemic Stroke in Young Women (odds ratio with 95% confidence intervals).

STUDY	OC Use	Women Without Migraine	Women With Migraine
Collaborative Group* [14]	No	1.0 (0.7-1.5)	2.0 (1.2-3.3)
	Yes	4.9 (2.9-8.3)	5.9 (2.9-12.2)
Tzourio et al. 1995 [16]	No	1**	3.7 (1.5-9.1)
	Yes	3.5 (1.5-8.3)	13.9 (5.5-35.1)

* Neighbour controls

** Reference category

The incidence of cerebral infarction in young women is low, however, and these relative risks must be kept in perspective. According to the literature, the annual incidence of ischemic stroke is approximately 4/100,000 for women aged 25-34, and 11/100,000 in women aged 35-44[24-26] although it may be higher in large American urban centres,[27] and considerably higher in American black women.[27] These global ischemic stroke rates include all women in a given age group, including migraineurs and OC users. An ischemic stroke rate can however be calculated for women who neither have migraine nor use OCs. We have done this using the following: 1) A migraine prevalence of 25% for women between 25 and 44;[28] 2) The assumption that 35% of females in these age groups were using OCs (in the study by Tzourio et al.[16] 36% of women in the control group were current users of oral contraceptives); 3) A relative risk for ischemic stroke of 3.5 for migraineurs as compared to non-migraineurs (see Table 1); 4) The assumption that use of OCs increases ischemic stroke risk approximately 3.5 times for non-migraineurs and migraineurs[16] (see Table 2).

With these calculations, the annual incidence for ischemic stroke in women who do not have migraine and who do not take OCs is approximately 1.3/100,000 for women aged 25-34, and 3.6/100,000 for women aged 35-44.

Can all this information on ischemic stroke incidence and relative risks for women with migraine and for OC users be put to practical use? We believe this information can be helpful in assisting decision making when the woman with migraine requests OCs. Given the information in the literature, the patient can now be presented with ischemic stroke risk figures which although approximate, can still be very helpful.

To be useful, it is not sufficient to simply divide women into migraineurs and non-migraineurs. There is ample evidence to indicate that stroke risk is much higher in patients who have migraine with aura (classic migraine) as opposed to those who have migraine without aura (common migraine)[29-31] (see also Table 1). In addition, as ischemic stroke incidence increases very significantly with age, the woman's age becomes an important factor in decision making.

We have tried to present this information in Table 3 in a form that will be useful. To construct this table, we have utilized the relative risks for ischemic stroke for the migraine subtypes as shown in Table 1 in the study from Tzourio et al. 1995, as this study utilized the International Headache Society diagnostic criteria for migraine. We have also utilized data from the same study (see Table 2) which indicated that OCs increased ischemic stroke risk approximately 3.5 times both for non-migraineurs and migraineurs. We have made the additional assumption that OCs increase ischemic stroke risk equally in both migraine with aura and migraine without aura. Although this assumption appears reasonable, specific data are not yet available in the literature on this point, and further research is urgently needed.

Table 3: Expected Incidence of Ischemic Stroke (Strokes per 100,000 women per year) in Women With and Without Migraine, With and Without OC use.*

Age	OC Use	Women Without Migraine	Women With Migraine	
			Without Aura	With Aura
25-34	No	1.3	4	8
	Yes	5	14	28
35-44	No	3.6	11	22
	Yes	13	38	78

* The values in the table must be regarded as approximate, and some assumptions have been made in their calculation. Please see text for details. Expected ischemic stroke rates are lower for women under 25, and higher for those over 44 than those shown here. In all categories, however, the presence of risk factors (smoking, etc.) will likely increase ischemic stroke rates above those shown here, whereas absence of such risk factors may result in ischemic stroke rates lower than those shown.

Although the data in Table 3 can serve as a guideline, each woman with migraine who is considering OC use must be evaluated individually. For example, low dose OCs may carry less risk, but the women with stroke in the 1995 Tzourio study[16] were taking relatively low dose estrogen preparations (estrogen dosage range 20-50 µg). Further, the presence of additional risk factors will significantly affect stroke risk. For example, in one comparison of non-smoking women, women with migraine had an ischemic stroke risk of approximately 5.8 times that of women without migraine. For women who had migraine and who also smoked heavily, the relative risk for ischemic stroke was 10.2 compared to non-migraineur non-smokers.[16]

Table 3, as is the case with the other tables, deals with ischemic stroke risk (cerebral infarction) only. Much less data are available for relative risk in migraine of hemorrhagic stroke. The Collaborative Group Study[14] did suggest that the incidence of hemorrhagic stroke might be increased slightly in

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migraineurs, but OC use appeared to add much less risk as compared to the case in ischemic stroke.

General Recommendations

1. In patients with migraine who wish to go on the pill, the risks and benefits of OC use should be discussed, and a joint decision made with the patient. It must be kept in mind that OCs are one of the most effective methods of contraception currently available, and that the medical, psychologic, social and economic consequences of pregnancy can be significant.[32] Although it may be necessary to err on the side of caution, the risks OCs might pose to the patient should not be exaggerated.
2. When patients with migraine are placed on OCs, the patient should be carefully monitored, both for increasing headache severity and frequency, for the development of new focal neurologic symptoms, or for significant change in neurological symptoms if the patient already has a migraine aura before starting OCs. Some changes, especially those involving new focal neurologic symptoms, may indicate an increased stroke risk for that particular patient over and above that expected for the patient's migraine category.

Specific Recommendations

1. Women with migraine without aura (common migraine) can probably use OCs with relative safety. However, if the patient has major risk factors for stroke (hypertension, smoking, etc.), or is over 34, use of oral contraceptives might not be appropriate, and careful evaluation is advised. For example, according to Table 3, a woman with migraine without aura who takes OCs for ten years starting at age 35 has a 1/263 chance of ischemic stroke during that time period.
2. For women in whom migraine attacks without aura become significantly more severe while on OCs, discontinuation of the pill should be advised. However, the decision as to how to proceed should be made in conjunction with the patient, and in many cases the advantages of remaining on the pill may outweigh the risks to the patient which are likely small. If the headache worsening is dramatic, the patient should be strongly advised to discontinue the OC.
3. Although women suffering from migraine with aura (classic migraine) are advised by some authors to use other forms of contraception,[33] it would seem inappropriate to consider the pill absolutely contraindicated in all women with migraine with aura. For younger women with the most common migraine aura, visual scintillations lasting less than 60 minutes, the low estrogen dose OCs might well be appropriate. On oral contraceptives, such patients would according to Table 3 have an expected ischemic stroke incidence of less than 28/100,000 women per year. The stroke risk might be considerably less in women under 30 who have only a simple aura. These stroke risks are lower than, for example, those to be expected in a woman over age 35 who has migraine without aura and who takes OCs.

   For patients with more complex migraine auras, it might be assumed that the ischemic stroke risk would be higher than in patients with simple migraine auras, although this assumption is based more on opinion than on objective data. Caution would be advised for patients who have more dramatic visual auras, such as complete hemianopsias lasting a significant period of time. Patients with focal numbness are also a concern, although in some patients these auras can be very mild and short. Unfortunately, clearcut risk figures are not available for patients of this type. I would not use OCs in patients with less common auras such as hemiparesis and transient dysphasia. In summary, OCs should be avoided in women with "moderate to severe neurologic events in migraine".[34] For women with migraine with aura who are over age 34 who use OCs, the risk of ischemic stroke becomes significant. According to Table 3, a woman in this category who takes OCs for ten years has a 1/128 chance of ischemic stroke during that time period.
4. Women with prolonged migraine auras (a focal neurological symptom lasting longer than 60 minutes) should not be placed on the pill. The pill is probably not advisable for women with multiple aura symptoms, even if no one symptom lasts more than 60 minutes.
5. If the patient develops a migraine aura for the first time on the pill, or if a previously mild typical migraine aura becomes more prolonged and complex, discontinuation of OCs should be advised.
6. OCs should obviously be discontinued in women with migraine who develop transient ischemic attacks, stroke, or evidence of ischemic vascular disease elsewhere.

Treatment of Migraine Headache in Patients on OCs

For patients whose migraine without aura attacks continue while on the pill, or who continue to have their usual migraine attacks with aura, with a typical short visual aura, standard symptomatic and prophylactic migraine therapy can be used as indicated.

As is often the case in women who are not on OCs, migraine attacks are often most severe and resistant to treatment around the time of menstruation. If such attacks do not respond to standard migraine therapy, other treatments used for menstrual migraine in patients not on OCs can be used for patients on OCs as well. These include the daily use of naproxen sodium or ergotamine suppositories in a prophylactic fashion beginning the day before headache vulnerability related to menstruation starts, and continuing through for five or six days until the period of headache vulnerability is over.[35]

Falling estrogen levels are likely the headache trigger for menstrual migraine.[36,37] The same likely is true in patients with menstrual migraine on OCs. Therefore, in women with menstrual migraine headaches not responsive to other measures who take OCs and who suffer marked disability from these headaches, low dose estrogen replacement during the menstrual period may be effective, as it is effective in patients with menstrual migraine who are not taking OCs.[38-40] The estradiol cutaneous patch is probably the best way of accomplishing this therapy.[41]

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