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# Hormonal Management of Migraine Associated With Menses and the Menopause: A Clinical Review

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**CME**

Objective.—This article reviews hormonal strategies used to treat headaches attributed to the menstrual cycle or to peri- or postmenopausal estrogen fluctuations. These may occur as a result of natural ovarian cycles, or in response to the withdrawal of exogenously administered estrogen.
Background.—A wide variety of evidence indicates that cyclic ovarian sex steroid production affects the clinical expression of migraine. This has led to interest in the use of hormonal treatments for migraine.
Methods.—A PubMed search of the literature was conducted using the terms "migraine," "treatment," "estrogen," "hormones," "menopause," and "menstrual migraine." Articles were selected on the basis of relevance.
Results.—The overarching goal of hormonal treatment regimens for migraine is minimization of estrogen fluctuations. For migraine associated with the menstrual cycle, supplemental estrogen may be administered in the late luteal phase of the natural menstrual cycle or during the pill-free week of traditional combination oral contraceptives. Modified contraceptive regimens may be used that extend the duration of active hormone use, minimize the duration or extent of hormone withdrawal, or both. In menopause, hormonally associated migraine is most likely to be due to estrogen-replacement regimens, and treatment generally involves manipulating these regimens. Evidence regarding the safety and efficacy of these regimens is limited.
Conclusions.—Hormonal treatment of migraine is not a first-line treatment strategy for most women with migraine. Evidence is lacking regarding its long term harms and migraine is a contraindication to the use of exogenous estrogen in all women with aura and those aged 35 or older. The harm to benefit balances of several traditional nonhormonal therapies are better established.

Key words: *migraine, menstruation, menopause, hormone, treatment*

Cyclic ovarian sex steroid production may affect the clinical expression of migraine, as demonstrated by a wide variety of clinical, epidemiologic, and basic science observations. Clinical observations include the fact that attacks of migraine in some women correlate with the menstrual cycle and improve when hormonal cycling ceases during pregnancy or after menopause.[1–6] Epidemiologic evidence includes the fact that migraine is more common in women than in men, with incidence peaking in the year of menarche.[3] Experimental evidence has established the influence of sex steroids on nociceptive and antinociceptive pathways known to be involved in pain and migraine.[7–11,12]

Based on quasi-experimental observations in a small number of women with menstrually triggered migraine, Somerville proposed that the late luteal phase decline in estrogen levels could trigger migraine. In women who predictably experienced migraine attacks around the time of the menstrual flow, he administered supplemental estrogen. Expected attacks of migraine were postponed until the effects of the supplement wore off. In contrast, progesterone supplementation was not effective in preventing menstrual attacks.[13–17] Subsequently, multiple lines of evidence have confirmed the validity of estrogen withdrawal, after periods of sustained high levels, as a migraine trigger in premenopausal women.

A study by Lichten et al supports estrogen withdrawal as a migraine trigger in postmenopausal women. He administered 5 mg intramuscular depo-estradiol to 16 postmenopausal women with migraine and 12 nonmigraineurs, and monitored estrogen levels and headache activity for the next 28 days. All women had been on estrogen replacement therapy prior to study entry. No woman experienced headache during the 14 days following the injection, but as estrogen levels declined, all 16 of the migraineurs developed headache, at an average of day $18.5 \pm 2.8$ and a serum level of $46.4 \pm 5.6$ pg/mL. No woman without migraine experienced headache during estrogen withdrawal.[18]

The most plausible explanation for estrogen withdrawal as a trigger for migraine is the hypothesis put forward by Welch et al of a "mismatch" between the timing of estrogen effects on gene regulation in the central nervous system, and its effects on cell membranes.[19] He suggests that under ordinary circumstances estrogen-mediated gene regulation "modulates inhibitory peptide function in the trigeminal nerve." This counterbalances estrogen-mediated increases in neuronal membrane excitability. When estrogen levels fall, their down-regulating effect on inflammatory genes is removed and compensatory mechanisms cannot always

be invoked quickly enough to avoid the possibility of headache in women who have "the neuronal excitability that is an inherent feature of the migraine-prone brain."[19]

It is thus not surprising that some women with migraine are particularly vulnerable to attacks during the late luteal phase of the natural menstrual cycle, the pill-free week of combined hormonal contraceptive regimens, or the perimenopause, to name just a few events that may be characterized by periods of estrogen decline after sustained high levels. This review focuses on hormonal strategies used to treat headaches attributed to the menstrual cycle or to peri- or postmenopausal estrogen fluctuations. These may occur as a result of natural ovarian cycles, or in response to the withdrawal of exogenously administered estrogen.

## DEFINING HORMONALLY ASSOCIATED MIGRAINE

It is difficult to be certain whether an observed temporal association between an individual migraine headache and a particular hormonal event is causal or coincidental. This is especially true in women with frequent headaches, in whom some headaches will occur in association with hormonal events by chance alone. The authors of a population-based study of young women with at least 2 migraines a month concluded that menstruation accounts for only "a small proportion of attacks in young women with frequent migraine."[20] If serum estrogen levels could be measured, it might be easier to identify a relationship between hormonal fluctuations and headache. However, direct measurement, through blood or urine tests, of the hormonal changes suspected of triggering headaches currently is impractical in clinical practice.

This practical diagnostic difficulty is the most important limitation of hormonal headache definitions in the International Classification of Headache Disorders (ICHD-II).[21] Table 1 summarizes ICHD-II definitions of hormonal headaches. In general, these bring welcome standardization to a field characterized by serious diagnostic inconsistencies and variability.[22] However, criteria for both menstrual migraine and estrogen withdrawal headache rely on vaginal bleeding as a surrogate marker of internal hormonal changes. They thus cannot be applied to women with a functioning hypothalamic-pituitary-ovarian axis but no uterus, or those who may have undergone procedures such as endometrial ablation, even though the mechanism of cyclically occurring headaches in these cases may be identical to that in menstruating women. In fact, the hormonal nature of such headaches cannot be satisfactorily reflected using ICHD-II, a logical inconsistency that should be remedied in future revisions.

In the case of menstrual-associated headaches, longitudinal diary information that demonstrates a consistent pattern of headaches in close temporal association to the period is necessary to corroborate the impression of a hormonal trigger and plan the timing of treatment. Candidate criteria for menstrual migraine that debuted in ICHD-II require that headaches meeting migraine criteria occur in 2 of 3 menstrual cycles during a 5-day window extending from 2 days before to 3 days after menses.[21]

ICHD-II distinguishes between "pure" menstrual migraine (PMM) and "menstrually-related migraine" (MRM). Its authors explain the distinction by asserting that "hormone prophylaxis is more likely to be effective for pure menstrual migraine." As no strong scientific evidence supports this statement, it seems possible that the authors may have meant that hormone prophylaxis is more *feasible*, *practical* or *successfully implemented* in PMM than in MRM. In PMM the hormonal trigger for every attack can be assumed and anticipated, making it easy to time and target treatment. In women with MRM, who are susceptible to non-hormonal triggers and by definition have more frequent migraine than women with PMM, it is less possible to be certain that hormonal treatment of a particular attack is required or accurately timed.

ICHD-II also recognizes a category of headache termed "Exogenous hormone-induced headache."[21] In keeping with the temporal associations required to diagnose other secondary headache disorders, criteria require that the headache begin or "markedly worsen" within 3 months of beginning exogenous hormones, and "resolve or revert to its previous pattern" within 3 months of stopping exogenous hormones.

However, despite strongly held beliefs and numerous anecdotal reports suggesting that exposure to contraceptive hormones can produce headache, the scientific evidence for this is not especially strong.[23,24] A major failing of many studies invoked to support such a link is that they do not distinguish between hormone exposure and hormone withdrawal; a great deal of evidence suggests it is the latter which produces headache.[25–28] Many such studies also do not distinguish between migraine with and without aura, even though there is reason to believe these 2 migraine subtypes may respond differently to high estrogen levels. High stable estrogen levels generally protect against headache, but may be provocative of aura.[29–32] Interestingly, though, there is no ICHD-II category for "exogenous hormone-induced aura."

Similar problems dog attempts to diagnose and classify headaches connected to the perimenopause or menopause. Here, too, there is uncertainty about whether it is hormonal exposure, withdrawal, or both that can trigger headaches.[33] Again, studies showing a connection between headache and use of hormonal replacement therapies (HRT) shed no light on the reason for that association and many do not distinguish among sequential, cyclic or continuous methods of administering treatments.[34–36] As with oral contraceptives, studies that have examined these regimens separately generally support the view that it is estrogen withdrawal rather than exposure that is responsible for headache.[37]

Discussions of "menopausal headaches" often consider headaches that occur during the perimenopausal transition along with those that occur after menopause. In fact, a distinction between these 2 life stages is clinically important in any discussion of headaches. Postmenopausal status in previously menstruating

**Table 1.—International Classification of Headache Disorders-II Criteria for Hormonally Associated Headaches[21]**

**A1.1.1 Pure menstrual migraine without aura**

Diagnostic criteria:

  A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura*

  B. Attacks occur exclusively on day 1±2 (*ie*, days −2 to +3) of menstruation in at least 2 out of 3 menstrual cycles

    and at no other times of the cycle

**A1.1.2 Menstrually related migraine without aura**

Diagnostic criteria:

  A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura*

  B. Attacks occur on day 1±2 (*ie*, days −2 to +3) of menstruation in at least 2 out of 3 menstrual cycles

    and additionally at other times of the cycle

**A1.1.3 Nonmenstrual migraine without aura**

Diagnostic criteria:

  A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura*

  B. Attacks have no menstrual relationship

**8.3.1 Exogenous hormone-induced headache**

Diagnostic criteria:

  A. Headache or migraine fulfilling criteria C and D

  B. Regular use of exogenous hormones

  C. Headache or migraine develops or markedly worsens within 3 months of commencing exogenous hormones

  D. Headache or migraine resolves or reverts to its previous pattern within 3 months after

    total discontinuation of exogenous hormones

**8.4.3 Estrogen-withdrawal headache**

Diagnostic criteria:

  A. Headache or migraine fulfilling criteria C and D

  B. Daily use of exogenous estrogen for ≥3 weeks, which is interrupted

  C. Headache or migraine develops within 5 days after last use of estrogen

  D. Headache or migraine resolves within 3 days

women is generally defined as the absence, for 12 consecutive months, of menstrual bleeding.[38] It is characterized by stable, low estrogen levels. In keeping with the importance of estrogen withdrawal as a headache trigger, the majority of women with hormonally influenced migraine report significant headache improvement after menopause.[2,34,39,40]

The perimenopause is characterized by a "change in ovarian hormones, feedback relationships, and clinical experiences beginning in women age 35-50 with regular flow and ending 1 year after the final menstrual flow."[41] Clinically, it is marked by increased variability in the length of menstrual cycles and missed menstrual periods.[42] Although one might expect that estrogen levels in premenopausal women decline smoothly and gradually during this transition, estradiol levels are in fact increased during the perimenopause, and often are higher than those of the premenstrual years.[43] Estradiol receptors also may be increased in tissues.[41] These factors probably explain the amply documented worsening of headaches during the perimenopausal transition, and

the fact that the average age of women in most headache clinics and clinical trials is in the 40s.[44] Estrogen declines markedly in the first year after the last menstrual period and then remain low and stable.

In contrast to premenopausal women, where exogenous hormone exposure largely consists of contraceptive regimens, both contraceptive and HRT regimens may be used in perimenopausal women. Since unintended pregnancy can still occur, some perimenopausal women will be on hormonal contraception, while others may begin to use typical hormone replacement regimens.[45]

## CHARACTERIZING HORMONAL HEADACHES

The question of whether hormonally triggered headaches are more severe or treatment-refractory than similar nonhormonally triggered headaches is important. Unusually severe or difficult to treat headaches sometimes are believed to warrant special or more hazardous treatment regimens than other headaches. Studies of

treatment-seeking women in specialty headache clinics generally suggest that hormonally induced headaches are more severe than others.[4,46,47] However, this is not clearly true in the general population of women with headache. In a population-based diary sample of 81 women, information from over 7000 diary days showed headache was more likely during 2 days before and the first 2 days of menstruation, but overall these headaches were not more severe than headaches at other times. Attacks that were classified as migraine were significantly more severe but the differences were small.[48] It also is not clear that hormonally triggered headaches respond less well to treatment than nonhormonally triggered headaches in population-based samples of women with migraine.

## TRANSLATING KNOWLEDGE INTO TREATMENT

There is no evidence that hormonal treatments for migraine are more effective or safer than nonhormonal treatments. Most hormonal treatments for migraine have been tested in case series or small clinical trials in selected populations that are inadequate to fully establish their harm to benefit balance. The long-term effects of additional or increased hormone exposure from these regimens are unknown. Total exposure to hormones increases significantly with extended duration regimens, although daily hormone exposure does not increase and there is no accumulation of hormones. A recent Cochrane report on extended duration or continuous contraceptive regimens concluded that "the long term health effects have not been documented."[49]

No hormonal treatment regimen has United States Food and Drug Administration (FDA) approval for a migraine or headache indication. Most importantly, because of the risk of ischemic stroke, treatment guidelines from 3 authoritative groups recommend against the use of estrogen-containing contraceptives in many women with migraine.[50–53] Results of the Women's Health Initiative Study have led to recommendations against the routine use of estrogen replacement therapy in most women.[54–56]

Thus, a diagnosis of hormonally associated migraine adds hormonal therapy to the list of possible headache treatments, but does not mean that treatment *must* be hormonal. Table 2 lists nonhormonal therapies that have been investigated specifically for the treatment of hormonally associated headaches. A number of these are drugs that already have FDA approval for a headache, pain or migraine indication, and for which there is a great deal of existing safety and efficacy information and clinical experience. Nonetheless, interventions for hormonal headaches that directly target the presumed hormonal trigger, rather than working on downstream events, have a powerful intellectual and emotional appeal for doctors and patients. Many women with migraine need or choose to use hormonal treatment for other conditions or for contraception, and for them hormonal treatment of migraine may be desirable. Finally, some women do not benefit from or cannot use nonhor-

| Table 2.—Selected Nonhormonal Treatment Strategies Studied for Hormonally Related Headaches |
| --- |
| Nimesulide[102] |
| M-chlorophenylpiperazine[103] |
| Triptans [104–112] |
| Prostaglandin inhibitors[113,114] |
| Biofeedback[115,116] |
| Acupuncture[117] |
| Bromocriptine[118] |
| Magnesium[119] |
| Naproxen[120] |
| Ergonovine[121] |
| Aspirin-Acetaminophen-Caffeine[122] |

monal treatment strategies for migraine, and trials of hormonal treatments may be defensible.

The overarching goal of all hormonal treatment regimens for migraine is minimization of estrogen fluctuations. In the case of migraine associated with menstruation in pre or peri-menopausal women, several treatment strategies are possible. Supplemental estrogen may be administered in the late luteal phase of the natural menstrual cycle or during the pill-free week of traditional combination oral contraceptives. Modified contraceptive regimens may be used that extend the duration of active hormone use, minimize the duration or extent of hormone withdrawal, or both. Some treatment regimens use drugs that eliminate ovarian cycling, with or without add-back estrogen, while others employ anti-estrogen drugs. In menopause, hormonally associated migraine is most likely to be due to estrogen-replacement regimens, and treatment generally involves manipulating these regimens.

## HORMONAL TREATMENT STRATEGIES FOR MIGRAINE ASSOCIATED WITH MENSTRUATION IN PRE- OR PERIMENOPAUSAL WOMEN

### Estrogen Supplementation With or Without Ovarian Suppression.—

Somerville tested his estrogen withdrawal hypothesis of migraine by using estradiol implants in 5 women with menstrual migraine, in an effort to avoid estrogen cycling. He reported that high estrogen levels were achieved but that the clinical effects on headache were unpredictable and that in fact some women seemed worse. In another study, he administered long-acting estradiol valerate to 2 women, and short acting estradiol benzoate to others. Based on results in these patients, he concluded that oral estrogen preparations were ineffective.[13,14,57,58] Smits et al compared a transdermal patch that delivered 50 $\mu$g of ethinyl estradiol per 24 hours with

placebo patches in 20 perimenstrual women with pure menstrual migraine. The trial used a randomized allocation scheme and was methodologically rigorous. Patches were applied during 3 successive menstrual cycles. Results showed no improvement in migraine duration or severity, and no decrease in analgesic or ergotamine use in the 2 groups overall, but a subgroup analysis showed a benefit in patients who had an exteroceptive temporalis muscle suppression test preditive of migraine.[59]

De Lignieres et al studied 20 women with menstrual migraine who had regular cycles. They defined menstrual migraine as attacks of migraine occurring during a window of 2 days before menstruation through the last day of the menstrual cycle, and required that women have a history of attacks in the last 12 cycles preceding study entry. The trial was double-blind, placebo crossover for 3 consecutive cycles, with random allocation to estradiol 2.5 g gel or placebo. This regimen was begun 18 hours before the expected attack, and continued daily for 7 days each month. Attack frequency, duration and severity were recorded, along with side effects. Twenty-six estradiol cycles and 27 placebo cycles were analyzed. Attacks occurred in 8 of 26 estradiol cycles (31%) and 26 placebo cycles (96%). This was a statistically significant difference. Attack severity and analgesic use was reduced in attacks that occurred despite estradiol treatment, compared with those that occurred during placebo treatment. No serious side effects were observed.[60]

Dennerstein et al also tested percutaneous gel estradiol administered for 7 days in 5 cycles (2 treatment cycles, 2 placebo cycles, and 1 nontreatment cycle). Subjects were 22 women with "recurring menstrual migraine. Eighteen women completed the study. Results showed significantly decreased migraine in estradiol-treated cycles compared with placebo.[61] An earlier trial using oral estrogen had disappointing results.[62]

Magos et al studied subcutaneous estradiol implants in 25 patients with menstrual migraine for up to 5 years, including periods with oral progestogens. Twenty-three patients "improved," and 20 (83%) became "completely or almost completely headache-free." The authors concluded that "suppressing the hormonal fluctuations associated with the ovarian cycle" could be helpful.[63]

MacGregor and Hackshaw performed a double-blind, placebo-controlled, randomized crossover study of estrogen supplementation in 14 women who experienced migraine during the pill-free interval of oral contraceptives. Subjects were treated with 50 $\mu$g estradiol patches during the entire pill-free interval for 2 cycles, and with placebo patches for 2 cycles. There was a trend toward reduced headache in the estradiol-treated cycles, but it was not statistically significant. Only 12 women completed the study. The authors suggested that further investigation was needed.[64]

A small case series and case report suggested that pharmacologic induction of menopause with add-back estrogen could be helpful in treating women with menstrual migraine.[65,66] Another larger case series reported that 17 of 29 patients with menstrual migraine were headache-free after use of a gonadotropin releasing hormone (GnRH) agonist and transdermal estradiol. Thirteen eventually underwent oophorectomy with continued use of transdermal estradiol. Recurrence of headache occurred in only 1 of 17 patients during the following year.[67]

These open studies all lacked controls. No methodologically rigorous study has been performed to study this treatment method in women who have menstrual migraine. Some light is shed on this question by a study performed in a mixed population of women. Martin et al administered a GnRH agonist alone and a GnRH agonist with add-back estrogen to women with migraine, some of whom may have had menstrual migraine. In that study, which was double-blind, randomized, and placebo controlled, minimization of serum estradiol fluctuations alone was not sufficient to prevent headache. Estradiol supplementation given after medical menopause was established decreased headache overall, but appeared to provoke headache during first 2 days after a patch change. The authors noted the paradoxical effect of estradiol both preventing and provoking headache, and concluded that small changes in estradiol levels during treatment of the patch "seemed to be provocative of headache."[68]

### Modified Contraceptive Regimens.—
Headache associated with oral contraceptives is largely confined to the pill-free week of the traditional 21 day active pill/7 day pill-free regimen.[69] One study reported that 70% of women complained of headache during the 7 day pill-free interval, compared with 53% during the active portion of the regimen. This difference was statistically significant. The high prevalence of headache likely reflects the specific and detailed symptom inquiries made during the study; we have no information on the severity or clinical impact of the problems.[27] The correlation of headache complaints with the pill-free portion of traditional oral contraceptive regimens has sparked interest in extended duration regimens (sometimes also termed "continuous" administration regimens) that minimize the number of episodes of hormone withdrawal that may trigger headache.[70] Other regimens also can induce amenorrhea, and are sometimes considered as treatment options for menstrual migraine. However, many of those regimens, such as danocrine or the GnRH agonist leuprolide, do not reliably interrupt ovulation and thus do not provide contraceptive benefits.[70] They also frequently cause hypoestrogenic side effects including decreased bone density and vaginal dryness.[71]

There are other reasons for the upsurge of interest in extended duration contraceptive regimens. It has been pointed out that the typical 21/7 oral contraceptive regimen, which produces monthly withdrawal bleeding, was developed not for health reasons but simply because "the manufacturer of orally active progestins was unwilling to supply them for any use that would be perceived to interfere with the normal menstrual cycle."[72] A pill regimen that produced monthly bleeding episodes mimicking the naturally occurring menstrual cycle was thus viewed as more culturally acceptable. In contrast to the traditional 21/7 oral contraceptive

regimen, a typical extended or continuous duration regimen consists of 84 active/6 or 7 pill-free days[73] and decreases the number of withdrawal bleeding episodes to 3 or 5 a year. Patient acceptance of contraceptive regimens that produce amenorrhea or reduce the frequency of withdrawal bleeding is generally high.[74] It varies with age, with older women having stronger preferences for less or no bleeding.[75]

Shortening the pill-free portion of hormonal contraceptive regimens has also been advocated, partly as a way to reduce estrogen withdrawal symptoms, but also because a shorter pill-free interval decreases the likelihood of ovulation from missed pills in low-dose contraceptive regimens.[76,77]

The first record of a clinical trial of an extended oral contraceptive regimen dates to 1977, when Loudon et al studied an 84/6 regimen of 50 $\mu$g ethinyl estradiol and 2.5 mg lynestrenol. As with most extended duration regimens, breakthrough bleeding was the most common problem encountered, but disappeared with continued use. Headache symptoms during the study were not systematically evaluated.[73]

Sulak assessed 50 OC users with menstrual-related problems during the pill-free interval and attempted to put them on an extended duration regimen of whatever contraceptive pill they were taking. She was able to stabilize 37 (74%) on an extended regimen (generally 6-12 weeks of active hormones followed by a 7 day hormone-free interval. Sixteen (26%) discontinued OCs or returned to their traditional regimen before they were stabilized. Of those who stayed on the extended regimen, all reported a decrease in menstrual-related problems, including headache. However, symptoms were not systematically assessed with diaries, surveys or calendars. Reportedly, one woman "continued the extended regimen because of the relief from migraines previously experienced during pill-free intervals. . ."[28]

Several recent trials of extended contraceptive regimens have suggested a beneficial effect on a number of typical premenstrual symptoms, including headache. However, migraine complaints have not been an endpoint of these studies, although information about "headache" was sometimes collected as part of adverse event reporting.[26,78]

Studies that have looked more carefully at the influence of extended duration regimens on headache suggest that although they may reduce headache problems in comparison to traditional regimens, they are not a panacea. Even with extended duration regimens, headache continues to be a common complaint and a frequent reason for OC discontinuation. Improvements in headache on these regimens are generally quite modest. In a recent trial of an 84/7 oral contraceptive with regimen of 30 $\mu$g ethinyl estradiol with 0.15 mg levonorgestrel, 21.5% of women who discontinued the trial cited headaches as the main reason for stopping. Only 59 of the 203 trial entrants completed the 1-year trial. Migraine was not an endpoint of this study, although information about "headache" was collected along with other adverse events.[79]

Relatively few randomized, controlled studies have directly compared extended duration or continuous contraceptive regimens with traditional regimens and even fewer have collected or reported information on headache. A recent Cochrane review found only 3 studies that reported on diary-collected menstruation-associated symptoms, including headache.[49] Cachrimanidou et al showed a decreased headache frequency in the continuous dosing group compared with traditional ($P > 0.05$).[80] Miller and Notter found that headache was "less severe" in women receiving a 49-day cycle regimen compared with those on a traditional cyclic regimen ($P = 0.04$).[81] However, Kwiecen et al did not find a significant difference in headache between the 2 groups.[82] Finally, Anderson and Hait reported that adverse event data showed fewer headaches in the continuous group than the cyclic group, although symptom information was not collected by diary (OR 0.7; 95% CI 0.5 to 1.0).[83]

One randomized, controlled trial was not included in the Cochrane article because it studied a transdermal, rather than an oral, contraceptive regimen. Stewart et al studied 239 women 18-45 who were randomly assigned in a 2 to 1 ratio to either the norelgestromin/ethinyl E2 transdermal patch in an extended regimen (weekly application for 12 consecutive weeks, 1 patch-free week, and 3 more consecutive weekly applications, $n = 158$) or a cyclic regimen (4 consecutive cycles of 3 weekly applications and 1 patch-free week, $n = 81$).[84] In this study, subjects recorded "the presence or absence of headache along with headache characteristics, such as nausea or sensitivity to light" in daily diaries that were reviewed at study visits. The authors make note of an increased prevalence of headache in the women assigned to the extended duration regimen, suggesting that "The higher incidence of adverse event reports of breast discomfort, nausea, and headaches seen in the extended group may represent an estrogenic effect in some women. It is also possible that women assigned to use the 'new' extended regimen were more aware of and more likely to report common side effects than were women using the more common monthly regimen."[84]

Headache frequency was a secondary endpoint in the Stewart study, and a detailed analysis of the headache data was published separately.[85] The title of this analysis – "Suppression of estrogen-withdrawal headache with extended transdermal hormonal contraception" – implies that the regimen had a beneficial effect on headache, although that was not the case. Rather, both the extended duration and traditional contraceptive regimens had a negative overall effect on headache, but the extent of worsening was less in the extended duration group, although this difference was not statistically significant. The extended group had a higher mean number of headache days than the cyclic group even during the first 3 weeks of treatment, leading the authors to suggest that randomization was not successful. It is important to note that the endpoint assessed in this study was "headache." Information necessary to determine whether these were migraine headaches or not was not reported, and there are likewise no data regarding the

severity or functional consequences of the headaches, or information about other endpoints such as analgesic consumption that might shed light on these matters.

The authors did note a decrease of headache days over time in both the extended and traditional groups, and suggested that this might reflect the fact that "... steady state delivery of exogenous hormones in transdermal hormonal contraception might play a role in suppressing hormonally triggered headaches, regardless of regimen." While that is plausible, it is also the case that such headache improvement occurs with continued use of traditional oral contraceptive regimens.[69] Much stronger evidence is needed to be certain that transdermal preparations are in fact less likely to produce headache than oral formulations. Additionally, the authors of this study did not provide information on study dropouts that would allow determination of whether dropout due to headache might account for apparent improvement over time. The principal author was contacted in an attempt to obtain this information, but at press time had not responded.

The abstract for the article states that "In a majority of women studied, compared with cyclic use, extended use of transdermal norelgestromin/ethinyl estradiol delayed menses and reduced the total incidence of mean headache days during the hormone-free interval."[85] However, this statement is open to misinterpretation. Since women on the extended regimen experienced only one hormone-free interval compared to the 4 hormone-free intervals of women on the traditional regimen, it is a foregone conclusion that the "total incidence" of headache "during the hormone-free interval" would be reduced.

Media reports of this study did little to clarify matters, announcing simply that "Contraceptive patches cut headaches."[86] In reality, though, the benefits of extended duration contraceptive regimens for menstrually triggered migraine or headache have not been unequivocally established, and safety concerns about transdermal contraceptive patches have been raised. In late 2005, the FDA added a warning to the drug label, in response to a study showing that patch users received 60% greater total exposure to estrogen than users of conventional OCs.[87]

## OTHER HORMONAL TREATMENTS FOR MENSTRUALLY TRIGGERED MIGRAINE

Two small studies have suggested that the estrogen receptor modulator tamoxifen might benefit women with menstrual migraine.[88,89] However, tamoxifen therapy is poorly tolerated even by women who must take it to prevent or treat breast cancer, and this suggests that long-term compliance with such treatment for migraine is likely to be poor. Much larger and longer duration trials would be needed in order to establish the efficacy and safety of this regimen. In addition, there is at least one case report suggesting that tamoxifen therapy may aggravate, rather than suppress migraine, perhaps because it is both an agonist and an antagonist depending upon the subtype of estrogen receptor at which it acts. Mathew et al reported a case of a 44-year-old woman with a history of menstrual migraine treated with chemotherapy followed by tamoxifen for breast cancer. Headaches ceased when chemotherapy interfered with menstrual cycles. When tamoxifen was initiated, migraine returned and the patient required both prophylactic and acute migraine therapy in order to tolerate the tamoxifen.[90]

In an open label trial, the modified synthetic steroid hormone danazol was administered for 25 days each month to 131 women with "hormonally related migraines." Headaches in 83 women were improved, 67 of whom experienced continued improvement while using it for 6 months.[91] As with tamoxifen, much larger and more rigorously conducted studies would be necessary to establish the place of this therapy among other treatment alternatives for menstrual migraine.

A randomized, placebo-controlled study by Burke et al evaluated the daily use of a phytoestrogen-containing combination product of "60 mg soy isoflavones, 100 mg dong quai and 50 mg black cohosh" for 24 weeks in 49 women with menstrual migraine. Results showed a statistically significant reduction in the average frequency of attacks from weeks 9-24 in the treatment group compared with the placebo group. Unfortunately, the mixture of ingredients makes it impossible to distinguish the effect, if any, of the phytoestrogen component of this treatment regimen.[92] Ferrante et al treated 11 women with what would be considered pure menstrual migraine by ICHD-II criteria with a combination of 2 phytoestrogens. The study lasted for 3 months and the 10 women who completed the study experienced a statistically significant decline in the average number of days of migraine compared to baseline. Since the study was open-label with no concurrent control group, it does not furnish especially strong evidence in support of the specific effect of phytoestrogens.[93]

## HORMONAL INTERVENTIONS FOR MIGRAINE ASSOCIATED WITH MENOPAUSE

The estrogen withdrawal theory of migraine implies that women may be vulnerable to an exacerbation in migraine in the perimenopausal years, when the orderly cycling of estrogen and progesterone secretion becomes more erratic, but that physiologic menopause, once it is established is likely to produce migraine improvement.

Unfortunately, many studies of headache and migraine in "menopause" include women who are perimenopausal and those who are postmenopausal. This makes it difficult to determine the true prevalence and impact of migraine, because the hormonal environment and resulting impact on migraine is likely to be very different during these times. By way of illustration, the title of a study by Obermeyer et al indicates it is a survey of menopausal symptoms, but in fact it evaluated Spanish women between the ages of 45 and 55 "because this is the interval during which most women become menopausal." Thus, the study (and likely many other similar studies) conflates symptoms of both the perimenopause and menopause. In this particular case, headaches were reported by 47% of the sample, with 10% indicating headache was their "most

troublesome symptom." Twenty-three percent indicated they had consulted a physician about headaches.

MacGregor et al interviewed women attending a menopause clinic and found that 57% reported headache. Twenty-nine percent had experienced a migraine within the preceding 3 months, and 80% of these women reported headaches occurred more frequently than once a month. Since women attending menopause clinics may be postmenopausal or perimenopausal, the high prevalence of migraine in this sample is not surprising.[94]

Relatively few studies make a clear distinction between menopausal stages, but those that do provide the most useful information. Neri et al found that almost 2/3 of 76 women with a history of migraine reported they had experienced significant headache improvement after menopause was established. However, women with migraine who had undergone surgical menopause had a much less favorable course. The authors concluded that abrupt surgical menopause appeared to worsen migraine.[5]

## HRT AND POSTMENOPAUSAL HEADACHE

As with menstrual migraine, contraceptive regimens or supplemental estrogen can be used during the perimenopause. Once menopause is established, hormonally connected headaches are likely to be related to hormone replacement regimens that are being used for other reasons. Specifically, women on older sequential or interrupted HRT regimens may experience migraine when withdrawal bleeding is induced. In addition to manipulation of HRT regimens that are being used for other reasons, the use of estrogen specifically to treat climacteric symptoms, including migraine, has been advocated for some time.[95,96]

Several trials have studied the relationship between various HRT regimens and headache or migraine, but there have been no trials in which HRT was evaluated specifically for the *treatment* of migraine. Nappi et al obtained 7 months of diary information in 54 subjects seeking evaluation of menopause who also had migraine. Information was collected on headache frequency, intensity and climacteric symptoms. Subjects were divided into those with migraine and those with episodic tension-type headache (ETTH). After a 1 month run-in period, subjects received transdermal estrogen for 28 days along with medoxyprogesterone acetate administered for the last 14 days or 0.625 mg of conjugated equine estrogens along with medroxyprogesterone acetate for the last 14 days. Attack frequency, days with headache and analgesic intake statistically significantly increased in the group receiving conjugated equine estrogens, although headache severity was unchanged. The group receiving transdermal estrogen experienced worsening of headache, but it was less pronounced than in the group receiving oral estrogens.[97]

Nand et al evaluated whether the dose of progesterone used had an impact on headache. In this study, 3 different doses of medroxyprogesterone in combination with estrogen were compared in 3 groups of women. Results showed no difference in adverse events, including headache, among the 3 regimens.[98]

Facchinetti et al studied 3 HRT regimens: continuous combined (estrogen and progesterone co-administered daily with no interruptions), sequential cyclical (estradiol for 21 days with progesterone from days 12-21) and sequential continuous (estrogen administered for 28 days and progesterone for the final 7-14 days). Results showed an increase in headache attack frequency and analgesic consumption in all groups, but the worsening was smallest in the group that received continuous combined therapy.[99] Continuous combined HRT regimens are believed to be relatively safe, although as with continuous contraceptive regimens, the long-term impact of increased hormone exposure is unknown.[100]

Thus, evidence suggests that all forms of HRT may have negative effects on migraine and headache complaints, but that the extent of worsening may depend on the particular regimen that is employed. Initiation of cyclic therapy may markedly worsen migraine, whereas continuous HRT may minimize these fluctuations and be less likely to aggravate migraine. Transdermal preparations may be less likely to aggravate headache than oral treatments. The clinical significance and impact of HRT-induced headaches is not clear; more research on this point would be useful, as would more work to identify subgroups that may be especially likely to experience worsening headache. Some groups of women with migraine may be especially sensitive to HRT headache side effects. Odmark et al compared 2 continuous combined HRT regimens, and found that a history of premenstrual syndrome predicted high headache complaints in women starting treatment.[101]

## CONCLUSION

Ovarian steroid cycles play an important role in modulating the expression of migraine in many women. From a clinical perspective, this means that manipulation of hormonal contraceptive or replacement regimens may sometimes have a beneficial effect on migraine. Because their long term harm to benefit balance has not been characterized, hormonal treatments are not first-line headache strategies for most women with hormonally associated migraine. They are most appropriate in women with migraine who have other medical indications for hormonal treatment and no contraindications to use. Such women include those under age 35 who have menstrual migraine without aura and desire contraception or treatment for endometriosis, or postmenopausal women with intolerable menopausal symptoms and no contraindications to estrogen replacement therapy,

*Conflict of Interest:* None

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