Hormonal Management of Menstrual-Related Migraine (2007)

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If we accept that three-quarters of migraineurs are women, and 70% of these have noticed menstrual association of their headaches, then simple math tells us that the majority of migraineurs have menstrual-related migraine (MRM).

Contemporary preventive strategies for menstrual-related headaches can be classified as (1) non-specific, non-targeted, (2) non-specific targeted, and (3) specific. Non-specific preventives raise the threshold for migraine in general, whereas specific preventives aim to prevent the discrete hormonal trigger associated with menstrual-related migraine (MRM). Non-targeted preventives are taken daily without regard to the menstrual cycle, while targeted preventives are taken only in proximity to the menstrual window.

The first category—non-specific, non-targeted—includes traditional migraine preventives (such as tricyclics or antiepileptics) that are taken throughout the menstrual cycle in hopes of extending their benefit to MRM. Nonspecific targeted strategies include scheduled, perimenstrual dosing of triptans or NSAIDs. As success with targeted strategies requires accurate anticipation of menses, women with irregular cycles are not good candidates for these options.

The premenstrual decline in estrogen concentration appears to be the key factor in triggering MRM, thereby presenting a potential target for prevention. Some specific—or hormonal—approaches have shown efficacy, however individual strategies and outcomes vary widely. For those who find these results confusing, I will point out that their success or failure can be explained by four key principles:

1. MRM is precipitated by a decline in estrogen concentration;
2. Progestogen concentrations do not play a significant role in precipitating MRM;
3. Adequately reducing or eliminating the premenstrual decline in estrogen prevents MRM;
4. Increasing the magnitude of the premenstrual decline in estrogen will exacerbate MRM;

It is important to consider concurrent or comorbid medical conditions, as different hormonal preventives present unique indications and contraindications that cannot readily be generalized from one hormonal approach to the next. For instance, severe endometriosis is an indication for induction of medical menopause with gonadotropin-releasing agonists, yet it poses a contraindication for the use of subcutaneous estradiol pellets. Although smoking and hypertension are among contraindications for use of oral contraceptives (OCs), they do not preclude therapy with menstrually-targeted estrogen. Furthermore, a number of frequent comorbidities of MRM—including dysmenorrhea, menometrorrhagia, irregular menses and endometriosis—are themselves indications for treatment with OCs.

Successful hormonal preventives share a common factor: they eliminate or sufficiently minimize the premenstrual decline in estrogen concentration that is associated with MRM.

A variety of readily available and generally well-tolerated hormonal regimens can accomplish this feat:

(1) Conventional OCs plus supplemental estrogen in the menstrual week.

Often the conventional advice has been to switch women to “low-dose” pills, but 96% of OC users in the US are already on “low-dose” (<50 mcg EE) pills. It was shown in the 1970s that a 50 mcg pill aggravated migraine, but even today’s weakest pills provide no benefit for MRM—as they are packaged—because the decline in estrogen that accompanies the switch to placebo pills is equivalent to the decline experienced in the natural menstrual cycle

(approximately 20-25 mcg EE). To convert an OC to a preventive for MRM, sufficient estrogen must be added back during the inactive pill week to prevent estrogen withdrawal migraine.

In our experience, limiting the decline to a 10 mcg EE equivalent is preventive. In a small open-label study of women with MM (and few headaches outside the menstrual window), we tested an OC containing 20 mcg EE on days 1-21, followed by 0.9 mg conjugated equine estrogens on days 22-28. All subjects responded with at least a 50% reduction in headache frequency, registering a mean reduction of 78%.

Examples of this overall strategy include:

Mircette® (a 20 mcg EE OC with desogestrel) at bedtime days 1-21, followed by Premarin® (or Cenestin®) 0.9 mg at bedtime days 22-28 (in place of the last week of the OC pack).

Cyclessa® (a 25 mcg EE OC with desogestrel (although triphasic in the progestin content, it is monophasic in its estrogen content) at bedtime days 1-21, followed by Premarin® (or Cenestin®) 1.25 mg at bedtime days 22-28.

Yasmin® (a 30 mcg EE OC with drospirinone) at bedtime days 1-21, followed by Premarin® (or Cenestin®) 0.9 mg twice daily, days 22-28.

If even lower estrogen concentrations are desired—perhaps in a patient with aura—the same strategy can be achieved with a parenteral combination:

NuvaRing® (a 15 mcg EE vaginal ring contraceptive with etonogestrel), inserted days 1-21, followed by Vivelle Dot 0.075 days 22-28 (the patch is applied on day 22, changed on day 25 and worn for 3.5 days each; two patches are needed for the 7-day menstrual week).

(2) Extended-cycle oral contraceptives (OCs).

A new trend in contraception involves prolonged suppression of ovulation. On this regimen, MRM is simply delayed, not eliminated. To prevent the estrogen withdrawal migraines on this regimen, adequate supplementation can be prescribed in the 13th week to limit the resultant decline in estrogen.

An example of this strategy is Seasonale® (a 30 mcg EE pill with levonorgestrel) taken at bedtime days 1-84, followed by Premarin® (or Cenestin®) 0.9 mg twice daily, days 22-28.

(3) Menstrually-targeted estrogen supplements.

Some women with contraindications to the use of OCs may still be candidates for targeted strategies using estrogen alone, such as perimenstrual administration of an estradiol patch.

The timing of this intervention is critical: in one study, an estrogen patch was applied just before the onset of bleeding and left in place for seven days (to limit the magnitude of the premenstrual decline in estrogen by coinciding with the nadir of estrogen concentration). The 0.1 mg patch was effective; however, lower doses of estradiol (0.025 mg or 0.05 mg) were insufficient to prevent MM. However, a recent study showed that when estrogen supplementation was begun earlier—starting 6 days before the first day of menstruation and continuing until day 2 of the cycle—an increased incidence of migraine was seen just after the estrogen supplement was stopped. In this study, the nadir of estrogen concentration occurred on day 2 of the cycle, so instead of supplementing for a few days before and after that nadir, the abrupt discontinuation of estrogen was followed by an estrogen-withdrawal migraine.

An example of this approach is Climara® 0.1 mg applied 1-2 days before menses. The patch is applied over the lower abdomen and left in place for one week.

Some trial and error may be involved in finding the ideal combination for an individual patient. Nevertheless, MRM remains the ideal setting for migraine prevention: we know when it's coming; we know what precipitates it; and we have sample closets replete with agents to remedy the presumed trigger.