

THE WOMAN WITH “MONTHLY” HEADACHES

E. ANNE MACGREGOR, MFFP, DIPM

Case History

This 40-year-old part-time secretary has a history of “sick headaches” since the age of 15 years. Attacks were infrequent when she was younger, except for a few months following a whiplash injury when she was 25 years old, but they have gradually increased over the last few years. For the last 4 years, she has noticed that the headaches occur with her menstrual period, although she usually has one or two additional headaches a month at other times of the cycle. Nonmenstrual headaches will last the better part of a day, but menstrual headaches can last up to 3 days. The rest of the time she is fit and well with no other medical complaints. Her menstrual periods are regular and she has some cramps, but the bleeding is not heavy. She took the combined oral contraceptive pill for a couple of years when she was younger and had noticed bad headaches in the pill-free week, which ceased when she stopped the “pill” to have her first child. She was sterilized after the birth of her third child.

She has sought help because although she can manage the nonmenstrual headaches with analgesics, the menstrual headaches do not respond so well to treatment, and she sometimes has to stay in bed for a day or so. She has not lost time from work, as her part-time status enables her to plan work around her monthly cycle. However, the monthly migraines are a source of friction between her and her husband, who often has to leave work early to collect the children from school.

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the author’s discussion.

- What is the most likely diagnosis and how would you sub-classify her headache type?

- Is any additional information required to confirm the diagnosis?
- What investigations should be done?
- How would you advise her with regard to the treatment and prevention of these headaches?

Case Discussion

Diagnosis

When a patient describes a long history of episodic “sick” headaches, the diagnosis is almost certainly migraine. She presents with a typical description of menstrually related migraine; that is, she has migraine attacks regularly in conjunction with her menstrual periods but has additional attacks at other times of the cycle. Most women who present with menstrual or menstrually related migraine are in their late 30s or 40s and are not using hormonal contraception, although a younger group of women present with migraine in the pill-free week of combined oral contraceptives, with attacks coinciding with the withdrawal bleed. It is also typical for women to have had migraine for many years but without the link with menstruation becoming apparent until the years leading up to the menopause. Many women with menstrual complaints, including headache, do not recognize that the attacks are actually migraine, and the condition is often underrecognized by patients and underdiagnosed by doctors.

A description of attacks, and a normal physical and neurologic examination, can confirm diagnosis of migraine. Diary cards, kept prospectively over three cycles, can confirm the relationship between migraine and menstruation—many women already keep a note of this in their personal diaries.

When asked, she gave a description typical for migraine without aura, with early symptoms of yawning and hunger, followed by headache associated with nausea, photophobia, and occasional vomiting. Physical and neurologic examinations revealed no relevant abnormalities.

It is important to ask why the patient is consulting now and, in her case, the effect of migraine on her life was the reason. A useful opening question is, “What does the migraine stop you from doing?”

Investigation

Many women expect some sort of investigation to be undertaken—either a test of their hormones or a brain scan. Neither is indicated on the basis of the history given, together with a normal physical examination. It is useful to reassure the patient that there is no need to undertake any tests, as the problem is associated with the normal hormone fluctuations; it is the individual’s sensitivity to these normal changes that results in migraine.

Management Strategies

Having confirmed the diagnosis of migraine, the first step is to provide effective acute therapy.

The questions to ask include the following:

- What is her current medication? Is she taking it optimally and would she benefit from an alternative?
- Could the frequency of attacks be reduced by identification and avoidance of nonhormonal trigger factors?
- Would she benefit from prophylactic treatment?

Providing effective abortive medication may be as simple as ensuring that she is taking her current medication to best advantage, or it may mean prescribing different drugs or nondrug treatments. Identification of nonhormonal trigger factors is important for management, even for women with pure menstrual migraine; that is, attacks occur only with menstruation and not at other times of the cycle. This is because most attacks are the result of several triggers building up over the cycle, and the menstrual trigger is the final one to trigger an

attack (Figure 6-1). Hence, a useful strategy for the first appointment is to discuss acute treatment and to provide the patient with diaries for three cycles on which to record attacks, the menstrual periods, and any relevant nonhormonal triggers as they occur, such as missed or delayed meals, lack of sleep, etc.

In her case, she was taking acetaminophen. I changed this to aspirin, which would also help menstrual cramps, together with domperidone, a peripheral dopamine antagonist available in Europe, since nausea was a problem. We discussed the option of a triptan if this initial treatment was ineffective.

I scheduled the follow-up visit for after three menstrual cycles in order to review the acute treatment and discuss the effect of any triggers that she found.

She found the aspirin/domperidone regimen helpful for controlling symptoms of nonmenstrual attacks but had needed a triptan for menstrual attacks. Although this worked very effectively, she needed to repeat the dose over 3 or 4 days because the symptoms would return. She felt that neck pain was probably worse before a migraine. Missed meals combined with lack of sleep were definite triggers, and she had managed to avoid a few attacks over the previous month by making sure that she ate regularly. Her diary confirmed that she had fewer attacks overall but still had migraine regularly starting on the first day of her period or the preceding day. Her cycle was between 26 and 29 days. Overall, she felt things had improved, but the menstrual attacks were still a problem.

We discussed options for perimenstrual prophylaxis. Nonsteroidal anti-inflammatory drugs can be useful for women with heavy painful periods, as they can reduce blood loss and treat cramps, particularly if started just before or at the onset of bleeding and taken for several days. She did not have a particular problem with periods other than mild cramps. Of note in her history is that she had experienced bad headaches in the pill-free week of combined oral contraceptives, suggesting that she may be sensitive to estrogen “withdrawal” as a migraine trigger. Therefore, I suggested a trial of perimenstrual estrogen supplements, using gel containing estradiol 1.5 mg, starting about 3 days before the expected onset of menstruation until the fourth day of bleeding. She asked about the risk of using estrogen. I told her that although long-term use of estrogens for hormone replacement therapy (HRT) is associated with increased risk of thromboembolic disease and breast cancer, there is no evidence of increased risk of any of these conditions when supplemental estrogens are used in women already producing their own estrogen; the risks appear related to use of estrogens in postmenopausal rather than premenopausal women. The difference between supplemental estrogen and HRT is important since many

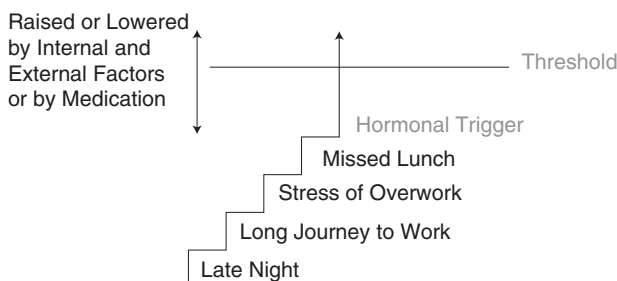


Figure 6-1. Triggers and the migraine threshold

women also ask about the need for additional progestin to protect the endometrium. This is not necessary provided that the woman is having regular menstrual cycles and is ovulating regularly. If there is any doubt, a mid-luteal phase progestin level can be checked.

KG tried supplemental estrogen for a further three cycles and found this to be a successful strategy. She found that the “menstrual” attack was shifted to about day 5 of the cycle, but it was not so severe. I gave her the option of continuing to supplement the estrogen until day 7 of the cycle, but since the aspirin and domperidone controlled the symptoms, she decided to continue with the gel.

We discussed the need for repeat review, particularly if her periods become irregular, since her present strategy could only be used while her periods remained regular.

Case Summary

This is a typical case of menstrually related migraine in a 40-year-old woman. As is usually the case, she had had migraine for many years, but other than when she experienced migraine with her “period” when she took the combined oral contraceptive pill, the association between migraine and her menstrual period had only developed over recent years. Menstrual attacks were longer and less responsive to treatment than nonmenstrual attacks. A combination of medications to control the symptoms of migraine and perimenstrual prophylaxis with estrogen supplements helped her to regain control of migraine.

Overview of “Menstrual” Migraine

Definitions

- Migraine associated with menstruation is typically migraine without aura, even in women who have a history of migraine with and without aura.
- Pure menstrual migraine:
 - Attacks of migraine occurring exclusively on day 1 ± 2 of menstruation (ie, days -2 to $+3$) in at least 2 of 3 menstrual cycles. The first day of menstruation is day 1 and the preceding day is day -1 ; there is no day 0.
 - No migraine at other times of the cycle
- Menstrually related migraine:
 - Attacks of migraine occurring on days 1 ± 2 of the menstrual cycle in at least 2 of 3 consecutive menstrual cycles
 - Additional attacks of migraine with or without aura at other times of the cycle

Extent of the Problem

Although migraine is a common condition in both sexes it is a greater problem for women than for men. Until puberty, migraine affects both sexes equally, but there is increased female predominance following menarche. This sex difference becomes greater with advancing years, peaking during the early 40s when migraine affects around 25% of women, compared with only 8% in men. Migraine is recognized by the World Health Organization (WHO) as being the twelfth leading cause in women of years of life lived with disability, whereas it is the nineteenth for men.

A study of women attending the City of London Migraine Clinic showed that nearly 50% of women subjectively associated migraine with menstruation. Menstrual attacks are reported to be more severe, of longer duration, less responsive to treatment, and with more recurrence than nonmenstrual attacks.

Mechanisms

Several studies have shown that the peak time for migraine during the menstrual cycle is within a couple of days before the start of a period and the first few days of bleeding. This is associated with, at least in some women, the normal “withdrawal” of estrogen in the late luteal phase of the menstrual cycle. Somerville noted that a period of estrogen “priming,” with several days of exposure to high estrogen levels, is necessary for migraine to result from estrogen “withdrawal.” Other studies have confirmed an association between migraine and estrogen “withdrawal” in situations such as the pill-free interval of combined oral contraceptives, postpartum, during the estrogen-free week of estrogen replacement therapy, and following estrogen challenge in postmenopausal women with a past history of menstrual attacks. Estrogen “withdrawal” migraine is without aura, even in women who have a history of migraine with aura.

However, estrogen is not the only hormone responsible for “menstrual” migraine. Other studies have shown that women who notice migraine during the first few days of bleeding may be susceptible to prostaglandin release during menstruation. Despite this clinical evidence for the effect of hormones on migraine, the pathophysiology remains poorly understood. Research is ongoing to assess other possible biochemical mechanisms. Identification of the underlying mechanisms will enable more effective treatment strategies to be developed.

Review of Drugs Used for Perimenstrual Prophylaxis

None of the drugs and hormones recommended below are licensed or governmentally indicated for management of menstrual migraine but can be prescribed on an individual patient basis.

Estrogen Supplements

Randomized clinical trials using percutaneous estrogen gel have shown efficacy. De Lignières and colleagues studied 18 women with strictly defined menstrual migraine, who completed a double-blind, placebo-controlled crossover trial using gel containing 1.5 mg estradiol (which allows a mean estradiol plasma level of 80 pg/mL to be reached) or placebo daily for 7 days during three consecutive cycles. Treatment was started 48 hours before the earliest expected onset of migraine. Only eight menstrual attacks occurred during the 26 estrogen-treated cycles (30.8%) compared with 26 attacks during the 27 placebo cycles (96.3%). Furthermore, attacks during estrogen treatment were considerably milder and shorter than those during placebo. Eighteen women also completed a similar trial by Dennerstein and colleagues, in which gel containing 1.5 mg estradiol or placebo was used daily for 7 days, beginning at least 2 days prior to the expected migraine, for four cycles. The difference between estradiol gel and placebo was highly significant, favoring the estrogen gel, and less medication was used during active treatment. However, the results were not as impressive as the study by De Lignières and colleagues. Dennerstein and colleagues commented that the reason for this might be that women in their study also experienced migraine at other times of the cycle, and therefore their migraine was only partially hormone dependent.

Nonsteroidal Anti-inflammatory Drugs

Mefenamic acid is an effective migraine prophylactic and has been reported to be particularly helpful in reducing migraine associated with menorrhagia and/or dysmenorrhea. However, no clinical trials have been undertaken specifically in menstrual migraine. A dose of 500 mg, 3 to 4 times daily, may be started 2 to 3 days before the expected onset of menstruation, but is often effective even when started on the first day of bleeding; this is useful if periods are irregular. Treatment is usually only necessary for the first 2 to 3 days of bleeding.

Naproxen has also been found to be effective in the management of headache associated with dysmenorrhea. Studies using 550 mg once or twice daily perimenstrually have shown efficacy.

Fenoprofen 600 mg has been tried, taken twice daily from 3 days before the onset of menstruation until the last day of bleeding.

Recent studies with perimenstrual triptans have proved promising, although the data are not sufficiently robust to warrant a general recommendation for use. One open study used prophylactic oral sumatriptan, given perimenstrually to 20 women who reported a predictable association between migraine and menstruation and who had shown a past response to sumatriptan. Some women reported

additional nonmenstrual attacks. In 126 sumatriptan-treated cycles, headache was absent in 52.4% and reduced in severity by 50% or greater in 42%. Despite these good results, prophylactic use of triptans is not recommended until results of double-blind, placebo-controlled trials confirm these findings.

A more recent double-blind, placebo-controlled study of prophylactic naratriptan 1 mg or 2.5 mg, given perimenstrually for 5 days, revealed that headache was absent in 23% of cycles in women using the 1 mg dose compared to a placebo response of 8%. Interestingly, naratriptan 2.5 mg was no more effective than placebo.

Data for frovatriptan taken for the 6 days from 2 days before the expected "menstrual" attack, also appear promising.

Continuous Hormonal Strategies

Perimenstrual estrogen supplements for migraine prophylaxis can be used only when menstruation is regular and predictable. If cycles are irregular, or when the above strategies prove ineffective despite a convincing hormonal link, then the following methods can be considered. Several of these regimens are contraceptive, which is often an additional requirement.

Combined oral contraceptives (COC) inhibit ovulation, producing fairly stable estrogen levels when taken. The use of such methods can improve migraine in some women, although the WHO does not recommend their use by women who have migraine with aura due to the potential increased risk of ischemic stroke.

Injectable depot progestogens inhibit ovulation, similar to the mode of action of COC. Only amenorrheic women became headache free, with other women reporting migraine associated with bleeding despite ovulation being suppressed. It is therefore important to warn women who use this method that they should persevere until amenorrhea is achieved, having earlier repeat injections than are required for contraception, if necessary.

Estradiol implants are the most effective method of obtaining high, stable estrogen levels. However, in hysterectomized women, progestogen opposition is necessary to protect the endometrium.

Gonadotropin-releasing hormones have been tried but adverse effects of estrogen deficiency, such as hot flushes, limit their use. The hormones are also associated with a marked reduction in bone density and should not usually be used for longer than 6 months without regular monitoring and bone densitometry. "Add-back" continuous combined estrogen and progestogen can be given to counter these difficulties. Given these limitations, in addition to increased cost, such treatment should be instigated only in specialist departments.

Hysterectomy has no place in the management of migraine alone. Studies show that migraine is more likely

to deteriorate after surgical menopause with bilateral oophorectomy. However, if other medical problems require surgical menopause, then the effects on migraine are probably lessened by subsequent estrogen replacement therapy.

General Recommendations for the Management of Menstrual Migraine

General Points

- Effective attack therapy is the mainstay of management and may be all that is necessary to provide adequate control.
- If attack therapy alone is not sufficiently effective, then prophylaxis may be indicated.
- A link between migraine and menstruation should be established using diary cards before considering specific therapy.
- The choice of prophylaxis depends on the regularity of the menstrual cycle, timing of attack in relation to bleeding, presence of dysmenorrhea and/or menorrhagia, presence of perimenopausal symptoms, and the need for contraception.
- Hormone prophylaxis is less effective for menstrually related migraine than for pure menstrual migraine.

First Visit

- Optimize attack therapy
- Provide diaries
- Discuss hormonal and nonhormonal predisposing factors and triggers
- If taking COC, carry out the following:
 - Migraine without aura only in pill-free interval (PFI): confirm with diaries and consider 3 to 4 consecutive packets (reducing PFI to 4 to 5 per year) or continuous COC use
 - Migraine with aura: change to progestogen-only or nonhormonal contraception
 - Worsening migraine since starting COC: consider change to progestogen-only or nonhormonal contraception
- Arrange review (usually after three menstrual cycles)

Second Visit

- Review efficacy of attack therapy and change as necessary
- Review diaries
 - Nonmenstrual migraine:
 - Consider standard prophylaxis if abortive therapy alone inadequate
 - Menstrually related migraine:
 - Consider anovulant hormonal contraceptives if contraception also required

- Consider hormone replacement therapy if symptoms suggestive of perimenopause
- Pure menstrual migraine:
 - Consider specific perimenstrual prophylaxis if periods regular and if abortive therapy alone inadequate
 - Consider anovulant hormonal contraception if periods irregular and/or contraception also required
 - Consider hormone replacement therapy if symptoms suggestive of perimenopause

Follow-up Visits

- Review efficacy of abortive therapy and change as necessary
- Review diaries
- Consider prophylaxis as indicated by symptoms and diaries

Selected Readings

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Editorial Comments

Dr. MacGregor has provided the reader with a remarkably lucid and helpful discussion and overview for any clinician

treating any woman with migraine associated with menses. The overview is helpful for acute treatment, and so-called mini-prophylaxis; that is, prevention aimed specifically at the menstrual period but not necessarily given the rest of the month. Some headache experts feel that giving progestational agents can make headaches worse, and some would use different approaches. However, read this chapter in detail, as it is most helpful in the advanced therapy of headache for this major trigger of migraine headaches.

FINAL DIAGNOSIS:

Menstrually related migraine without aura