Migraine is a common condition, affecting 15% of the population in the UK. After menarche, women have an increased prevalence of migraine compared to men, with a 3:1 female to male preponderance. In the World Health Organization’s estimates for Global Burden of Disease between 2000-2012, migraine ranks as the tenth highest cause of years lost due to disability. Women often relate their migraine and headache symptoms to their menstrual cycle, and there is evidence that migraines and headaches around the time of menstruation are often longer, more severe and more resistant to treatment than attacks at other times. Menstrual migraines are more likely to relapse, and are more disabling than attacks at other times of the cycle. It is also known that the relationship of migraines to hormones may change over a woman’s reproductive lifetime, with first attacks around menarche, fewer migraines during pregnancy, and migraines often resolving after menopause. This article will focus on hormonally related migraines in the pre-menopausal woman.

Migraines around the time of menstruation are usually without aura. The third edition of The International Classification of Headache Disorders (ICHD-3 beta) offers criteria for pure menstrual migraine (coded A1.1.1) and menstrually related migraine (coded A1.1.2), but both definitions are listed in the Appendix of the document due to uncertainty over whether they should be regarded as separate entities.

The importance of distinguishing between pure menstrual migraine without aura and menstrually related migraine without aura is that hormone prophylaxis is more likely to be effective for the former. Documented evidence, recorded contemporaneously, over a minimum of three cycles, is necessary to confirm the diagnosis, because many women over-report an association between attacks and menstruation. Useful diary cards can be downloaded from http://www.nationalmigrainecentre.org.uk/wp-content/uploads/2014/09/NMC-monthly-diary.pdf

There is some evidence that menstrual migraine attacks, at least in some women, result from oestrogen withdrawal, although other hormonal and biochemical changes at this time of the cycle may also be relevant. When pure menstrual migraine or menstrually related migraine is considered to be associated with exogenous oestradiol withdrawal, both codes – A1.1.1 pure menstrual migraine without aura or A1.1.2 menstrually related migraine without aura, and 8.3.3 Oestrogen withdrawal headache – should be used.

**Prevalence**

More than 50% of women with migraine, both in the general population and presenting to specialist clinics, report an association between migraine and menstruation, although fewer than 10% of women fit the criteria for pure menstrual migraine. Recent work has confirmed the presence of a long-suspected genetic basis for menstrual migraine.
Treatment options

Acute treatment of menstrual migraine is the same as for non-menstrual attacks and includes a combination of analgesics with or without prokinetic antiemetics, nonsteroidal anti-inflammatory drugs, and triptans. The regime described below is recommended by the British Association for the Study of Headache in the BASH Guidelines 2010. 

- **Step one: simple oral analgesic ± anti-emetic**
  
  Recommended analgesic doses for acute migraine are typically greater than standard doses to achieve rapid therapeutic levels against a background of gastric stasis:
  
  - Over-the-counter analgesic ± anti-emetic:  
    - For pain:  
      - aspirin 600-900mg or  
      - ibuprofen 400-600mg  
      - ± metoclopramide 10mg or domperidone 10mg.
  
  - **Step two: rectal analgesic ± anti-emetic**
    Diclofenac suppositories 100mg (up to 200mg in 24 hours) for pain.
  
  - **Step three: specific anti-migraine drugs, i.e. the triptans.**
    These are selective 5-hydroxytryptamine (5HT) receptor agonists, which were specifically developed to treat migraines. Any of the triptans can be used, according to patient preference and local prescribing guidance. None of the triptans has a licence specifically for the treatment of menstrual migraine, however, frovatriptan is particularly useful due to its longer half-life. Several trials have compared triptans in menstrual migraine, and frovatriptan has shown similar efficacy to others in terms of pain relief at two hours and at 48 hours. The relapse rate was significantly lower following treatment with frovatriptan (27%) vs the comparators (40%) (P<0.001).

Across all clinical trials, frovatriptan was well tolerated, with a low incidence of drug-related adverse events. These findings support the use of frovatriptan as a first line treatment for both the acute treatment and for perimenstrual prophylaxis of menstrual migraine.

Prophylaxis

As menstrually-related migraines tend to be longer and more severe than other migraines, many women request prophylactic treatment as well as good acute management for any breakthrough attacks. It is important to ascertain the needs of the patient in terms of contraception during the discussion about preventative treatment as some of the treatments involve hormonal manipulation, for example with contraceptive pills or oestrogen replacement. Many are not suitable if a pregnancy is planned in the near future.

Perimenstrual prophylaxis is indicated for patients with predictable menstrual migraine who wish to use preventative treatment. There are no licensed options, but choices include non-steroidal anti-inflammatory drugs, triptans and hormone manipulation.

Heavy or painful periods increase prostaglandin release and this, in turn, can trigger migraines in susceptible women. Blocking the prostaglandins can be an effective preventative for menstrual migraine in these women. Mefenamic acid 500mg tds, with food, started a couple of days before expected menstruation and continued through the heavy days can be useful. This should be tried for three cycles to assess efficacy.

Although few studies have examined naproxen for intermittent prophylactic treatment of menstrual migraine, some evidence supports its use for intermittent prophylactic therapy. A small study in 2007 examined use of naproxen in 25 patients with menstrual migraine. These patients took 550mg of naproxen daily for seven days before and seven days after the start of mense and kept a record of their headaches during this time. This timeframe was later narrowed to five days before and five days after the start of menses. If the cycle is unpredictable, then these drugs can be started on the first day of menstruation.
Menstrual migraine has been associated with the natural falls in oestrogen levels during the late luteal phase of the menstrual cycle, and also during the hormone-free interval of combined hormonal contraceptives. Oestrogen is a neuroactive steroid, influencing the pain processing networks involved in the process of migraine. Serotonin-producing neurons are sensitive to the presence or absence of oestrogen. As serotonin is implicated in migraine pathophysiology, this association with oestrogen is thought to account for the increased risk of migraine around the time of the fall in oestrogen levels. It also gives a theory for the efficacy of triptans for perimenstrual prophylaxis.

Data from randomised controlled trials for perimenstrual prophylaxis show a significant reduction in risk of menstrual migraine in women using frovatriptan for six days compared with placebo, with no evidence of delayed or rebound headache following treatment. NICE Headache guidance states: “For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5mg twice a day) or zolmitriptan (2.5mg twice or three times a day) on the days migraine is expected.”

Although steady or increasing levels of oestrogen may reduce the risk of migraine (i.e. pregnancy and menopause), acute migraine attacks may be triggered by significant drops in oestrogen levels. Reducing the magnitude of decline in oestrogen concentrations in female migraineurs of reproductive age prevents menstrually-related migraine (without aura). This can be achieved by taking exogenous oestrogens perimenstrually. Although not licenced for this indication, Oestradiol 1.5mg in 2.5g gel is available as a metered dose via a pump dispenser. One metered dose should be applied from day three and continued daily until the fifth day of bleeding. If this delays migraine, one metered dose of gel can be continued for two further days. The gel should be applied below the waistline, usually on the thighs or buttock, spread thinly over the skin. As per the advice in the product literature, it should not be used on or near the breast, as there have been reports of breast swelling, enlargement and pain, and benign breast neoplasm. Some patients prefer to apply an oestrogen patch instead of the gel and this is simply patient preference. Cutaneous administration of exogenous hormones offers fewer peaks and troughs in serum levels of hormone than oral administration. Oestrogen replacement is most suited to patients with a regular, predictable cycle. As with any treatment, the efficacy should be assessed over three cycles using symptom diaries. If headaches and migraines are exacerbated, then the treatment should be discontinued.

In patients without a regular cycle, or in whom there is a requirement for contraception, the contraceptive pill can be very useful. The UK Medical Eligibility Criteria 2009 rates the use of the combined contraceptive pill in patients with migraine without aura at any age as UKMEC 2 (i.e. the benefits outweigh the risks of use when used for contraceptive purposes alone). It could be argued that the benefits of migraine prevention further tip this balance in favour of use. The falls in oestrogen levels during the pill-free interval when using the combined oral contraceptive can trigger migraines, so tricycling of the combined oral contraceptive pill is often recommended. Patients can simply be advised to take two or three pill packets back-to-back, with no pill-free interval. This reduces the number of attacks over a year, and offers effective contraception as well as the benefits of predictable menstruation and associated migraine. Alternatively, a low dose combined oral contraceptive such as loestrin 20 can be used continuously. Many women experience some spotting with this regime, and if this occurs, then they should omit the pills for three days to allow a withdrawal bleed. As the pill free interval is shortened, they are at lower risk of developing migraines due to falls in oestrogen levels.

Using the progestogen-only pill can suppress the background hormonal fluctuations, and therefore stop menstrual migraines in women who have an oestrogen withdrawal migraine. This is often the preferred hormonal treatment in women who experience aura at other times in their cycle, as the combined oral contraceptive is classed as UKMEC 4 in patients with aura (i.e. a condition which represents an unacceptable health risk if the contraceptive method is used). This is due to the increased risk of stroke in young women with aura. Taking the combined oral contraceptive further increases this risk and therefore it is not recommended when there are other, safer methods of contraception available. The progestogen only pill is rated UKMEC 2 and therefore the benefits outweigh the risks.

There is also some evidence for the use of magnesium supplements in the prevention of menstrual migraine. A small randomised, double blind study comparing magnesium 360mg per day with placebo, showed that the number of days with headache was reduced only in the patients on the active drug. Magnesium treatment also improved premenstrual complaints, as demonstrated by the significant reduction of Menstrual Distress Questionnaire (MDQ) scores. The authors claim that their work supports the possibility that a lower migraine threshold could be related to magnesium deficiency.

If these targeted preventative methods for menstrual migraine are not effective, or if there are significant numbers of migraines at other times in the cycle, then a more standard prophylactic regime can be effective. NICE recommends topiramate or propranolol in the first instance. Women starting on topiramate must use effective contraception as it is contraindicated in pregnancy. Propranolol is considered safe in pregnancy, however the risks and benefits of continuing prophylaxis through pregnancy must be discussed.
Migraine in pregnancy
Commonly, migraine will improve throughout pregnancy. Patients can be reassured that migraine does not increase the risk of foetal abnormalities, miscarriage or stillbirth. Acute attacks can be treated with aspirin and an anti-emetic in the first and second trimester, and with paracetamol in the third trimester. Although the use of triptans during pregnancy is not recommended in the product literature, the recent NICE evidence update for headache states that triptan use in pregnancy is not associated with miscarriage, stillbirth or congenital malformations.16

Follow up
Patients should be encouraged to try each regimen for three cycles to assess efficacy, while keeping detailed symptom diaries. Even if a preventative regime is effective, the underlying migraine pattern can change, so continuing migraine prophylaxis should be reviewed six months after the start of prophylactic treatment.11

BOX 2: CASE STUDY
A 38 year old woman with a 20-year history of migraines with and without aura presents with monthly attacks of migraine without aura which is particularly debilitating and no longer responding to her usual treatment with sumatriptan 50mg orally. Her diary cards reveal a menstrually related migraine pattern, with occasional attacks of migraine with aura between menstrual periods. She is treated with cerazette (progestogen only pill, or POP) and given aspirin 900mg and metoclopramide 10mg to treat acute attacks. She is also prescribed frovatriptan 2.5mg to take if the initial acute treatment does not relieve her symptoms within 45 minutes.

At review, three months later, she has become almost amenorrhoeic on the POP, with only occasional breakthrough spotting and associated migraines. She reports that these have been easier to treat than previously and she is happy with her acute medication.

References

KEY POINTS
1. Diagnosis of menstrual migraine and menstrually-related migraine is by three months of symptom diaries
2. Offer acute treatment according to the BASH stepped approach:
   1. Prokinetic antiemetic with simple analgesia, e.g. metoclopramide 10mg and aspirin 900mg
   2. Rectal analgesic, e.g. diclofenac 100mg and antiemetic
   3. Triptan, e.g. frovatriptan 2.5mg
3. Consider prophylaxis with perimenstrual medication
   1. NSAID, e.g. mefanamic acid 500mg tds or naproxen 250mg bd
   2. Prophylactic frovatriptan 2.5mg daily
   3. Oestrogen as oestradiol 1.5mg in 2.5ml gel daily from three days prior to menstruation
4. Consider other hormonal methods, particularly if contraception required
   1. Tricycling or continuous use of combined oral contraceptive (if no history of aura)
   2. Progestogen only pill
5. Consider other means of migraine prevention, particularly if migraines occur at other times in the cycle, e.g. magnesium supplements, propranolol or topiramate