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Mini review

Perimenopausal migraine in women with vasomotor symptoms

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ABSTRACT

Migraine is affected by fluctuating estrogen levels so it is not surprising that the perimenopause is a time of peak rate of change of migraine prevalence in women. Evidence supports estrogen 'withdrawal' as one of the important triggers of menstrual attacks of migraine without aura, while high levels are associated with migraine aura. This mini review addresses the issues of diagnosing migraine, treating the symptoms of migraine, and controlling co-morbid migraine and hot flushes with hormonal and non-hormonal options. Maintaining a stable estrogen environment is the most effective treatment for vasomotor symptoms and can also benefit estrogen-withdrawal migraine. Using only the lowest doses necessary to control symptoms minimizes the risk of unwanted side effects. Non-hormonal options for both conditions are limited but there is evidence of efficacy for fluoxetine and venflaxine, with less evidence for gabapentin.

1. Introduction

Migraine is a common problem during the perimenopause. In studies of women attending menopause clinics, between 24% and 29% had migraine [1]. Despite being associated with significant disability, migraine is often underreported and underdiagnosed. With simple diagnostic tools and a better understanding of how to manage migraine, healthcare providers can combine effective management of vasomotor symptoms with safe and effective management of migraine.

2. Diagnosing migraine

The two main types of migraine are migraine without aura, which accounts for around 70–80% of attacks, and migraine with aura, which accounts for around 20–30% of attacks. About 1% of attacks are of aura alone with only a very mild or absent headache (migraine aura without headache) but a careful history usually reveals past episodes of migraine with or without aura. The International Headache Society (IHS) has published a classification of migraine and other headache disorders, now in its second edition [2]. While these are useful to ensure homogeneity in clinical trials, they are not always practical in the clinical setting. Migraine can more simply be considered as recurrent episodes of disabling headache, lasting 4–72 h associated with nausea and photophobia in an otherwise well person. Diagnosis based on these key features is simplified by using the validated screener I-D Migraine (Fig. 1). When used in the primary care setting this had a positive predictive value of 0.93 (95% CI, 89.9–95.8) [3].

The diagnosis of aura often causes confusion but is important since aura is a marker that the individual is at increased risk of ischaemic stroke [4]. The key features are the duration of symptoms and timing in relation to headache (Fig. 2) [5]. When asked to describe the symptoms, patients frequently draw azigzag in the air, representing typical scintillations of migraine aura. Incontrast to these specific features of aura, generalized 'spots before the eyes', 'flashing lights', blurring of vision or photophobia of variable duration before or with headache often accompany migraine, particularly during the premonitory 12–24 h and should not be diagnosed as aura.

3. Pathophysiology of perimenopausal migraine

Throughout the reproductive years, menstruation is one of the most significant risk factors for migraine without aura, while postmenopause is associated with improvement in migraine. Research suggests that one of the prominent triggers of migraine in women is the natural fall in estrogen in the late luteal phase of the menstrual cycle [6]. If estrogen 'withdrawal' triggers migraine, then maintenance of a stable hormonal milieu should be associated with fewer migraine attacks. In accordance with this hypothesis, several studies have used perimenstrual estrogen supplements to maintain mid-luteal levels until the follicular rise in estrogen, successfully preventing menstrual migraine [7]. During the perimenopause it is not unusual for migraine attacks to become more frequent and severe as hormone levels fluctuate erratically. Irregular periods prohibit perimenstrual treatment so standard migraine prophylactic drugs are usually recommended. However, many women with migraine experience marked vasomotor symptoms that would also

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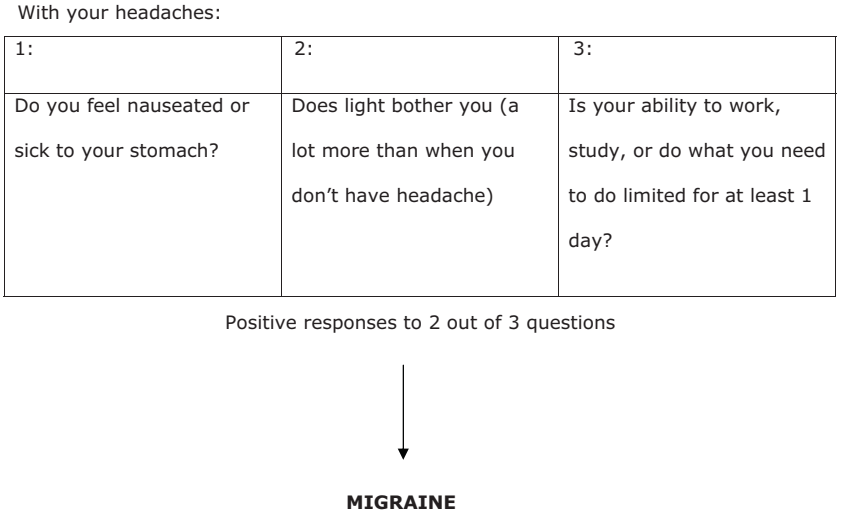


Fig. 1. ID Migraine.
Ref: Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: the ID Migraine validation study. Neurology 2003;61(3):375–382.

benefit from treatment. In these cases, management of vasomotor symptoms and migraine can be combined.

4. Assessment

Of pivotal importance is to ensure the correct diagnosis. Headaches are not mutually exclusive and a marked increase in headache frequency in a woman with a history of one or two attacks a month is an alert for further questioning. It is particularly important to ask about treatment of headache as use of symptomatic drugs more than 2–3 days a week can result in medication-overuse headache (MOH), with daily or near daily symptoms. Drug withdrawal is necessary as headaches are refractory to most other treatment strategies. The European Federation of Neurological Societies (EFNS) management guidelines are useful if MOH is suspected [8].

An invaluable assessment tool is a symptom diary (Fig. 3). This can be used to aid diagnosis, assess the relationship between migraine, menstruation and vasomotor or other symptoms, and assess efficacy of treatment.

5. Acute treatment of migraine attacks

Acute treatment of attacks is the mainstay of migraine management since preventive strategies are rarely more than 50–60% effective at reducing the frequency and/or severity of symptoms. Several national guidelines outline the variety of treatment options available [9,10]. Over-the-counter drugs can be effective, provided that they are taken in adequate doses and preferably in a soluble or effervescent formulation. Aspirin 900–1000 mg has similar efficacy to sumatriptan 50–100 mg [11]. Codeine and other opioids should be avoided as they aggravate gastric stasis and nausea.

6. Management of migraine and vasomotor symptoms

There is no evidence that treatment of vasomotor symptoms in women with migraine should differ from standard recommendations, including use of HRT. Lifestyle changes alone or combined with a non-prescription treatment, such as isoflavones may be considered, although evidence of efficacy is limited. Weight loss should be encouraged [12,13].

There are several pharmacological options that have clinical trial evidence of efficacy for both migraine and vasomotor symptoms (Table 1). The most effective pharmacological approach of vasomotor symptoms is with hormone therapy (HT). Non-oral routes, such as patches or gels, are also less likely to have a negative effect on migraine than oral formulations of estrogen replacement [14,15]. This is probably the result of the more stable serum hormone levels associated with non-oral routes. If oral preparations are favoured, tiboloneis the preferred option [16]. Estrogen should

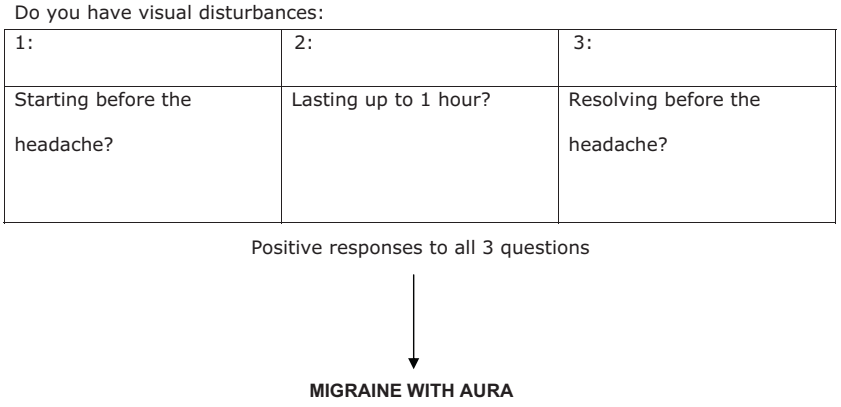
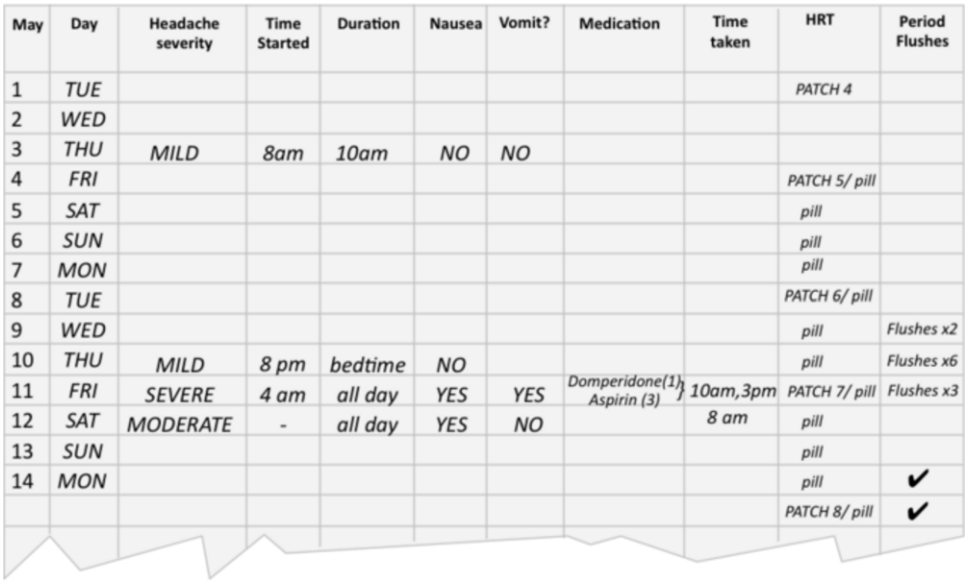


Fig. 2. A simple screen for migraine with aura.
Ref: Gervil M, Ulrich V, Olesen J, Russell M. Screening for migraine in the general population: validation of a simple questionnaire. Cephalalgia 1998;18:342–348.



May	Day	Headache severity	Time Started	Duration	Nausea	Vomit?	Medication	Time taken	HRT	Period Flushes
1	TUE								PATCH 4	
2	WED									
3	THU	MILD	8am	10am	NO	NO				
4	FRI								PATCH 5/ pill	
5	SAT								pill	
6	SUN								pill	
7	MON								pill	
8	TUE								PATCH 6/ pill	
9	WED								pill	Flushes x2
10	THU	MILD	8 pm	bedtime	NO				pill	Flushes x6
11	FRI	SEVERE	4 am	all day	YES	YES	Domperidone(1) Aspirin (3)	10am,3pm	PATCH 7/ pill	Flushes x3
12	SAT	MODERATE	-	all day	YES	NO		8 am	pill	
13	SUN								pill	
14	MON								pill	✔
									PATCH 8/ pill	✔

Fig. 3. Migraine diary.

be given continuously to prevent estrogen 'withdrawal' migraine [17]. The dose and route of delivery of estrogen replacement should be assessed to provide the lowest effective dose necessary to control menopause symptoms.

A perimenopausal woman with an intact uterus requires endometrial protection. Licensed premenopausalHT strategies typically recommend cyclical progestins for 12–14 days a month. However, continuous administration of estrogen and progestin appears to be better tolerated by migraineurs than cyclical combined HT [18]. Although standard continuous combined HT is only licensed for postmenopausal women, the levonorgestrel intrauterine system can be used as a continuous progestogen component of HT. This is well tolerated as a result of its local endometrial action and enables the dose of estrogen to be adjusted according to symptoms while ensuring endometrial protection. It has the additional advantage of providing effective contraception.

Migraine aura, with or without headache, is not a contraindication for estrogen replacement when using non-oral routes and low doses of natural estrogens, which have little effect on thrombotic parameters. This is in contrast to the prothrombotic effects of synthetic contraceptive estrogens, which are generally contraindicated. If aura starts for the first time it is necessary to exclude a transient ischemic attack or other migraine mimics, particularly in a woman with no history of migraine. If aura is confirmed but does not resolve, re-assess following a reduced dose or withdrawal of estrogen, considering non-hormonal strategies as indicated.

Alternatives to HT for management of vasomotor symptoms include fluoxetine, venlafaxineandgabapentin [19,20]. None of these are as effective for controlling hot flushes as estrogen. Fluoxetine and venlafaxine also have evidence of efficacy for migraine prophylaxis [9,10]. Initial exacerbation of migraine in the first few weeks of treatment can occur, which settles with continued use, so it is important not to stop treatment too early [21]. Gabapentin can also be used for migraine prophylaxis, although evidence of efficacy is far from robust [9,10]. Higher doses are necessary for migraine management than for the control of hot flushes [19].

7. Research agenda

Exacerbation of migraine during the perimenopause is a common clinical problem. The relationship between vasomotor symptoms and migraine, and identification of a common pathophysiology that could target improved management, are prime candidates for research.

Given the unpredictable fluctuations and wide range of estrogen levels in women approaching menopause, management of premenopausal women with vasomotor symptoms and migraine is more challenging than management postmenopause. There is the added requirement of effective contraception premenopause. Contraceptive pills containing natural estrogens is an interesting research area, as these have the potential to control estrogen

Table 1
Recommended options for pharmacological management of vasomotor symptoms in women with migraine.

Treatment		Dose
Hormone therapy		
Hysterectomised women	Continuous transdermal estrogen (patch or gel)	
Non-hysterectomised women: premenopause	Continuous transdermal estrogen plus LNG IUS	
Non-hysterectomised women: postmenopause	Continuous transdermal estrogen plus LNG IUS Continuous combined patches Estrogen gel/patch plus continuous oral progestogen Tibolone	Use lowest effective estrogen dose to control vasomotor symptoms
SSRIs	Fluoxetine	20 mg daily
SNRI	Venlafaxine	75–150 mg daily
GABA analogue	Gabapentin	900 mg daily in three divided doses

GABA, γ-aminobutyric acid; IUS, intrauterine system; LNG, levonorgestrel; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

'withdrawal' migraine and menstrual disorders, while also providing a contraceptive form of HT.

8. Conclusion

Migraine is a common disorder, particularly prevalent in women. Perimenstrual estrogen 'withdrawal' is a recognized trigger for migraine without aura. During the perimenopause, unpredictable fluctuating estrogen levels are associated with deterioration in migraine without aura, often coupled with vasomotor symptoms and irregular periods. Hormone therapy can be optimized to manage hot flushes effectively with potential benefit on estrogen 'withdrawal' migraine. Non-hormonal options with evidence of efficacy include fluoxetine and venlafaxine. There are a number of research areas worth exploring to assess the common pathophysiology and management of these conditions.

9. Practice points

- Women often do not spontaneously report migraine as a menopause symptom.
- Perimenopausal migraine may benefit from treatment of co-existing vasomotor symptoms
- Use the lowest effective dose of estrogen necessary to control vasomotor symptoms, in a non-oral route.
- In non-hysterectomised women, a continuous combined regimen is better tolerated by women with migraine than cyclical regimens.
- Non-hormonal treatments, including SSRI/SNRIsor possibly-gabapentin, can also help migraine but are not as effective at controlling vasomotor symptoms as estrogen.
- Migraine exacerbated by perimenopausal hormone fluctuations has a good prognosis post menopause.

Contributors

E. A. MacGregor is the sole author.

Competing interest

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