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LITERATURE REVIEW

Menstrual Migraine : How Hormones Impact Migraine

Restu Susanti¹, Syamel Muhammad²

Affiliation author : 1. Neurology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang; 2. Sub Division of Oncology Gynecology, Obstetrics and Gynecology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang

Correspondence to: Restu Susanti, Hp: 085274490010

Abstract

Menstrual Migraine is divided into 2 subtypes: Menstrually Related Migraine (MRM) and Pure Menstrual Migraines (PMM). In PMM symptoms do not occur outside the menstrual cycle while MRM, symptoms can occur at other times apart from the menstrual cycle. The occurrence of menstrual migraines is related to the female hormones cycle in the form of the decrease in estrogen levels which usually occurs a week before the onset of menstruation. The mechanism is unclear, but it is thought that a decrease in estrogen levels can trigger decrease in serotonin levels, causing cranial vasodilation and sensitization of the trigeminal nerve.

Keywords: *menstrual migraine, hormones*

INTRODUCTION

Headache is the most common symptom in daily life, about 90% of every individual has experienced headache at least 1 time per year. Most of patient who come to neurologist complaint about their headache. A study in Medan in 2003 found that headache was ranked first with a percentage of 42% from 10 most common diseases.¹

Migraine is a type of primary headache that is classified by the International Headache Society (IHS) and is the second most common primary headache after Tension Type Headache (TTH). According to the International Headache Society (IHS), migraine is recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine. Migraine can be familial disorder with characteristics of episodic headache attacks with different intensity, frequency and length.³

Migraine is 18% more common in women. The onset often occurs in the teens with a peak incidence at the age of 35-45 years. Migraine is caused by several factors such as hormones, nutrition, weather, stress, stress, emotional, olfactory stimulation (cigarette smoke, perfume and others), lack of sleep, excessive sleep, fatigue and physical activity. About three to four sufferers report that their migraines are caused by specific factors and sometimes the causes appear together, such as stress, lack of sleep, and menstruation.⁴

Migraine occurs in nearly 30 million people in the United States and 75% of them are women. Migraine can occur at any age but usually appear at the age of 10 - 40 years and the



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rate of occurrence decreases after the age of 50 years. Migraine incidence double after puberty and increases again in middle age in women. Estrogen is thought to play a role in this disease. Estrogen fluctuations are migraine trigger. Migraine can occur before or during menstrual periods (where there is a large decrease in the estrogen), during pregnancy or menopause, and when women take hormonal drugs, such as oral contraceptives and hormone replacement therapy.⁵

DEFINITION OF MENSTRUAL MIGRAINE

Based on The International Headache Society menstrual migraine divided into two subtypes, pure menstrual migraine without aura and menstrually related migraine without aura. Menstrually related migraine without aura must have onset during the perimenstrual period (2 days before up to 3 days after menstruation) and this pattern must be confirmed in 2/3 of the menstrual cycle, but other attacks can occur at other times of the menstrual cycle. On the other hand, in pure menstrual migraine without aura the migraine attacks are limited to the peri-menstrual period and don't occur at other times of the month.⁶

Box 2 International Headache Society classification of pure menstrual migraine and menstrually related migraine²

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 \pm 2 (i.e. Days +2 to -3)¹ of menstruation² in at least two out of three menstrual cycles and at no other times of the cycle

Notes:

1. The first day of menstruation is Day 1 and the preceding day is Day -1; there is no Day 0.
2. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy.

A1.1.2 Menstrually-related migraine without aura

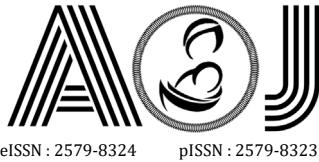
Diagnostic criteria:

- A. Attacks, in a menstruating woman, fulfilling criteria for '1.1 Migraine without aura'
- B. Attacks occur on Day 1 \pm 2 (i.e. Days -2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle

Notes:

1. The first day of menstruation is Day 1 and the preceding day is Day -1; there is no Day 0.
2. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy.

Picture 1. International Headache Society Classification of Pure Menstrual Migrain and Menstrually Related Migraine.⁷



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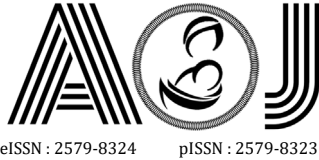
Based on clinical research, around 20-60% of women who experience migraine are reported to have an association with menstruation.⁸ The prevalence of menstrual related migraine without aura is 35-51 % and pure menstrual migraine is 7-9% in women with migraine according to American Headache Society. Menstrual migraine first appear at the age of 5-19 years, and mostly occur in women at the age of 30 to 40 years.

ETIOPATHOGENESIS OF MENSTRUAL MIGRAINE

The pathogenesis of menstrual migraine is associated with the different effects of male and female sex hormones.¹⁰ The menstrual migraine trigger is the decrease in estrogen levels that occurs just before and during menstrual period. Other factors which also contribute in its pathophysiology are: 1) release of prostaglandins from *endometrial decay* which sensitize peripheral nociceptors, 2) decrease in serum magnesium levels, and 3) decreases in inhibitory neurotransmitter systems (ie, serotonergics, GABAergics, etc.) which modulate the neuron from the trigeminal system. Social factors, including stress, sexual harassment, and history of bad childhood experiences can also contribute to higher migraine incidence in women.¹¹⁻¹⁶

The risk of migraine is very high during the first three days of menstruation when there is a noticeable change in estrogen levels. In 1972, Somerville and colleagues proposed the "estrogen withdrawal" hypothesis, which states that a decrease in estrogen levels before menstruation can trigger menstrual migraine attacks. The decrease in estrogen levels can increase neuron sensitivity to prostaglandins and neuropeptide release such as CGRP, P substances and causing neurogenic inflammation.¹⁷ This occurs during the late luteal phase of the natural menstrual cycle and during hormone-free intervals in combined hormonal contraception.¹⁸ Decreased estrogen levels that occur during the final luteal phase of the menstrual cycle can be correlated with decreased serotonin production and increased estrogen elimination, leading to cranial vasodilation and trigeminal nerve sensitization, which can trigger migraine. Other systemic symptoms, such as headaches and nausea, accompanying menorrhagia and or dysmenorrhoea can occur when excessive prostaglandins enter the circulation.^{12,19}

In some cases, female patients may also experience migraines during regular ovulation. A woman may be sensitive to the small decrease in estrogen that occurs about 12 days before menstruation begins.¹⁰ Increased aura events are associated with high estrogen levels. On the other hand, low estrogen levels during menstruation are unlikely related to aura.¹⁹ However, migraine will not be triggered by stable or increased estrogen levels. By eliminating estrogen withdrawal, estrogen supplements can be used to prevent menstrual migraines.^{19,20}



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There are two sub-types of menstrual migraines, menstrually related migraine and pure menstrual migraine, with the first being more common than the second. The characteristic of menstrually related migraine menstruation are migraine without aura that occur one to the day before or after menstruation and occur in more than 60 percent of the cycle and migraine attacks can occur at other times in the cycle. Whereas, pure menstrual migraine are migraine without aura that occur exclusively for one or two days before or after menstruation and occur in more than 60 percent of the cycle. Pure menstrual migraines only occur in about 10 percent of women with menstrual migraines which makes it less common than menstrually related migraines.²¹

Compared with all other phases of the menstrual cycle, migraine attacks without aura are most likely to occur during a "five-day window" that starts 2 days before menstruation and continues until the first 3 days of menstruation. Studies show that more than 70 percent of women are more likely experience migraines in the two days before menstruation and 2.5 times more likely to experience attacks during the first three days of bleeding.²²

Menstrual attacks are longer, more severe, are more likely to recur, are less responsive to treatment, and are associated with greater disability when compared to attacks at other times of the cycle.²²

DIAGNOSIS OF MENSTRUAL MIGRAINE

There are no tests to confirm the diagnosis of menstrual migraine, although tests can be done to rule out headaches due to other causes. Based on research migraine attacks appear between 2 days before menstruation and 3 days after menstruation.²³

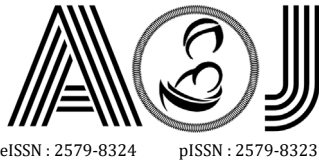
Pain is a very subjective symptom and varies by individual. To be able to make the right diagnosis requires carefulness in the patient's history. To make it easier to diagnose migraine, migraine diagnosis criteria are used according to the International Headache Society (IHS).²⁴

Pure Menstrual Migraine Without Aura

Diagnostic criteria:

Attacks, in a menstruating woman¹, fulfilling criteria for *Migraine without aura* and criteria on below:

Occurring exclusively on day 1 ± 2 (*ie*, days -2 to $+3$) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle.



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Diagnostic criteria:

Attacks, in a menstruating woman¹, fulfilling criteria for *Migraine without aura* and criteria on below :

Occurring on day 1 ± 2 (*ie*, days -2 to +3) of menstruation in at least two out of three menstrual cycles, and additionally at other times of the cycle.

Migrain Wihout Aura

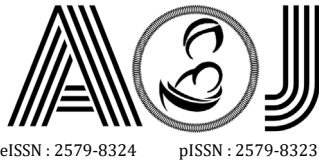
Diagnostic criteria:

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
 1. unilateral location
 2. pulsating quality
 3. moderate or severe pain intensity
 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D. During headache at least one of the following:
 1. nausea and/or vomiting
 2. photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis.

MENSTRUAL MIGRAINE MANAGEMENT**A. Short-Term Prophylaxis for Menstrual Migraine**

For many women, menstrual migraine is more difficult to treat. The attacks usually last longer and are more severe. In general, the treatment for menstrual migraines is the same as non-menstrual migraine. If migraine frequency is rare, NSAIDs alone (or with paracetamol) or in combination with triptans, may be very helpful.²⁵ NSAIDs are also useful for treating menstrual cramps. If migraine is frequent, predictable, prolonged or less responsive to therapy, consider short-term prophylactic treatment. In this situation, long-acting triptans, frovatriptan or naratriptan 2.5 mg twice daily, recommended for 3-5 days. Treatment is limited to no more than 6-8 days per month to avoid the risk of overdose.²⁶ Triptans can be started in combination with NSAIDs 2 days before the expected menstrual date (in patients with regular cycles) or during prodromal phase.²⁷

Another approach is to increase the dose of regular preventive medications, such as topiramate or amitriptyline 5 days before menstruation. Adding 500 mg of magnesium starting from ovulation until after menstruation can prevent or reduce the severity of



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migraine attacks. Menstrually related migraine with aura is most often seen in high estrogen states, such as in combination of hormonal contraception or hormone replacement therapy.²⁸

B. Other Prophylactic Options for Menstrual Migraine

For those who suffer from PMM and MRM, a possible approach is to suppress ovulation by using.^{29,30}

- Desogestrel-only progesterone (POP) pills. Other POPs act primarily through the cervical mucosa and are unlikely to suppress ovulation. POP is safe in those who suffer from migraine with aura.
- Progesterone injections (depo-provera) which is given every 12 weeks
- Progesterone implant (implanon) which lasts for three years.

It is possible to partially or completely suppress the menstrual cycle by using COCP (Combined Oral Contraceptives Pill) without rest for 63-84 days (3/4 package 21 days without monthly break). It is acceptable to continue the 63-84 day cycle for several years. The side effect is increased body weight.

C. Choice of Oral Contraception

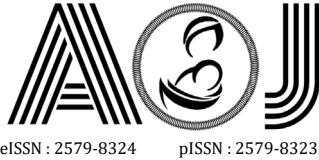
There are three types of oral contraceptives: fixed-dose, triphasic, and progesterone-only pills. The use of triphasic oral contraceptives can increase migraine due to repeated hormonal changes and should be avoided if possible. It is recommended to use low-dose estrogen products for COCP. There are usually fewer side effects and lower incidence of migraine compared to higher dose pills. Many women may experience migraine when using COCP for the first time. COCP is contraindicated in smoking women who suffer migraine with aura due to fifth times higher risk of ischemic stroke.³² COCP should be stopped in women with menstrual migraine when:

- The frequency and or severity of migraine increases
- There is onset of new aura
- There is unusual or prolonged migraine

POP (Progesterone Only Pills) is the contraceptive of choice in migraine, for example desogestrel in women with PMM. However, there may be side effects including bleeding and weight gain. Bleeding can be reduced by increasing the dose of progesterone to two tablets daily.^{30,31,32}

CONCLUSION

Menstrually related migraine without aura must have onset during the perimenstrual period (2 days before up to 3 days after menstruation) and this pattern must be confirmed in 2/3 of the menstrual cycle, and other attacks can occur at other times of menstrual cycle.



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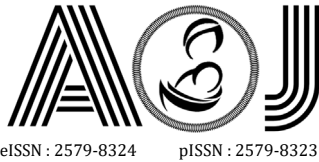
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While in pure menstrual migraine without aura the migraine attack is limited to the perimenstrual period and does not occur at other times of the month.

The risk of migraine is very high during the first three days of menstruation, when there is a noticeable change in estrogen levels. There are no tests to confirm the diagnosis of menstrual migraines, although tests can be done to rule out headaches due to other causes. For many women menstrual migraine are more difficult to treat. In general, the treatment is the same with nonmenstrual migraines. If migraines occur infrequently, NSAIDs or the combination of NSAID with triptan can be given. The use of NSAID can also be useful for treating menstrual cramps.

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