# Special Issues in Managing Migraine in Women: A Review Article

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#### Abstract

Migraine is a highly prevalent condition experienced by women throughout their child bearing age, started from menarche to menopause. It is affected by the oestrogen, female hormonal changes especially during menarche, pregnancy and menopause. Women with migraines have an increase risk for stroke during pregnancy as well as other vascular complications.

Treatment should be considered based on the severity of the patient's headache and functional disability. It is important to select the safest and appropriate therapy especially during pregnancy. Sometime migraine treatment is essential in view of increase maternal and foetal risks resulting from acute attacks rather than the potential adverse effects of therapy itself. Non-pharmacologic treatments are preferred because only a few drugs are safe to use during pregnancy and lactation.

Key words: Menstrual Migraine, Pregnancy, Lactation, Menopause, Hormone

### Introduction

Migraine is a common headache which is usually associated with nausea, photophobia and impaired daily activities. Generally it can affect up to 25% of women with childbearing age.<sup>1</sup> About 15% of the general population can affect migraine with a male: female ratio of about 1:1 in prepuberty and 1:3 in post pubertal age.<sup>2</sup>

In the US the incidence of migraine without aura is highest in girls of age between 14 and 17 years however for migraine with aura, the highest incidence is between 12 and 13 years.<sup>3</sup>

Female hormone, oestrogen mainly influences migraine attack in female. Migraine occurs frequently when oestrogen level changes in menarche, menstruation, pregnancy, and menopause. Prevalence of migraine is increasing after menarche.<sup>4</sup> Studies have found a significant relation between migraine, abruption placenta, preeclampsia and stroke during pregnancy.

### Pathophysiology of migraine in women

The pathogenesis of migraine is still a debated issue. Recent biochemical studies report the metabolic abnormalities in the synthesis of neurotransmitter and neuromodulator. The resulting metabolic shift directs tyrosine metabolism towards the decarboxylation pathway with unphysiological production of noradrenalin, dopamine together with increased synthesis of amines such as tyramine, octopamine and synephine. The unbalance levels of neurotransmitters and neuromodulators in the synaptic clefts of the pain pathway may activate the trigeminal system releasing calcitonin gene-related peptide. This induces inflammation and dilation of meningeal blood vessels that causing headache and related symptoms.<sup>5,6</sup> Migraine attack is actually a top-down dysfunctional process starts in frontal lobe propagating downwards the pain nuclei.

One of the triggering factors to initiate migraine in women is the changes in levels of oestrogen. Migraines especially develop when oestrogen level changes occur during menstruation, pregnancy, and menopause.

Attacks of migraine without aura are particularly associated with decline in oestrogen level. In contrast, the migraine with aura is usually affected by high oestrogen level in the blood.<sup>7,8</sup> In pregnancy, migraine without aura is predicted to be improved because of high placental oestrogen level. Studies showed that 60% to 70% of migraineurs improve migraine during pregnancy and 20% completely cease migraine attacks.<sup>9</sup>

### Migraines in women

Attacks of migraine in women can be discussed in following categories;

- 1 -- Menstrual migraine
- 2 -- Migraine in pregnancy and puerperium
- 3 -- Postpartum migraine
- 4 -- Migraine during lactation
- 5 -- Migraine in menopause
- 6 -- Migraine and oral contraceptive
- 7 -- Migraine and hormonal replacement therapy

### **Menstrual Migraine**

Menstrual migraine accounts 60 % of women with headache. It usually develops in adult life, at the age of menarche. It reaches a peak at the age of forty and attack is reduced at menopause.<sup>10,11</sup>

Pure menstrual migraine (PPM) accounts 10% to 14% of women with migraine which entirely occurs on days 1- 2 (i.e., days -2 to +3 of menstruation) in at least two out of three cycles and at no other time of the month.<sup>12</sup> Migraine attacks which occur at other times of the menstrual cycle usually last longer with poor respond to treatment.<sup>13</sup>

# **Classification of menstrual migraine [MM]**

Menstrual migraine, as defined by the International Headache Society, has two subtypes<sup>1</sup>

1. Menstrually related migraine without aura

Attacks of menstrually related migraine without aura must have an onset during the perimenstrual time period (2 days before to 3 days after the onset of menstruation) and this pattern must be confirmed in 2/3 of menstrual cycles, but other attacks may occur at other times of the menstrual cycle.

2. Pure menstrual migraine without aura

Those are similar to the above criteria except that migraine headaches are strictly limited to the peri-menstrual time period and do not occur at other times of the month.

### Migraine in pregnancy and puerperium

Most studies showed that women with migraine improve from first to third trimester of pregnancy.<sup>14</sup> This feature is especially found in women with migraine without aura and those who had menstrual migraine. Majority of migraine which occur first time in pregnancy are migraine with aura.<sup>9,15-17</sup> Vascular events such as gestational hypertension, preeclampsia and ischemic strokes are more found in women with migraine.<sup>18</sup>

# Postpartum Migraine

About 30-40% of women with age of 30 years or less usually develop relapse of migraine attack after delivery.<sup>19-21</sup> One of the study reported that the median time to onset of headache was 2 days and duration was 4 hours. Migraine without aura accounts for 6.3%, but migraine with aura is only 1%.<sup>21,22</sup>

# **Migraine during lactation**

One study reported that relapse of migraine occurred in 100% of women with migraine during the first postpartum month and 43.2 % in women with breast feeding.<sup>16</sup> It is postulated that low levels of oestrogen in lactating period trigger the attack. Breast feeding should be advised in women with migraine.

### Migraine in menopause

Studies found that migraine attacks became worse around peri-menopausal period. However it is usually ceased after menopause. Compare to natural menopause, surgical menopause has a higher risk of migraine.<sup>23</sup> In post-menopausal women with HRT, the effects of HRT on migraine attacks are varied depending on the type and forms of oestrogen used, and mode of administration. Short course of HRT is found to be beneficial; however the full course of HRT may worsen migraine.<sup>24-26</sup>

# **Migraine and Oral contraceptives**

Combination oral contraceptives (COCs) may trigger not only new migraine attack in women but also cause worsening migraine attack in those with a previous migraine.<sup>27-29</sup>

Studies showed that 18-50% of cases with migraine developed increasing migraine frequency and severity and improvement was found in 3-35% of cases. About 39-65% of cases had no significant changes. Women of migraine with aura have more deleterious effects of COC than those with migraine without aura.<sup>30</sup>

### Migraine and hormone replacement treatment (HRT)

There is a strong association between migraine and hormonal fluctuations, especially of decline in oestrogen level in the blood during menstrual cycle. This impact of oestrogen on migraine becomes more obvious during perimenopausal period.

Hormone replacement therapy is generally accepted both in post menopausal women with or without migraine. HRT especially trigger and increase attacks of migraine headache. However studies showed that majority of women with migraine were improved with HRT; only a minority of women report no change or worsening attack.<sup>28,31,32</sup> In addition, on-oral form oestrogen shows more effective than oral oestrogen.<sup>26</sup>

# Treatment of migraine

Early initiation of treatment is essential for effective management. If the treatment is being delayed, the effectiveness of medications is reduced, with a greater likelihood of nausea and the attack may last longer than it might otherwise.

### Non pharmacologic treatment

Non-pharmacologic treatment has a significant benefit with minimal risk to mother and foetus.<sup>33</sup> Trigger factors should be controlled by regular exercise, adequate sleep; avoid high intake or withdrawal of coffee and good hydration. Biofeedback and acupuncture have been found to be effective.<sup>34,35</sup> Non-pharmacologic approaches should be considered first, but preventive treatment should be initiated if they are not effective.

# Pharmacological treatment

#### Menstrual migraine

Before initiation of migraine therapy, a headache diary should be recorded for 3 months to ensure menstrual related headache. Women with menstrual migraine who have three or more debilitating headaches per month or poor response to migraine medications, either

hormonal and/or non-hormonal prophylactic therapy may require. Non-hormonal therapy includes some antiepileptic, B-blockers, calcium channel blockers and antidepressants. Those drugs should be initiated 5 to 7 days before and during menstruation. Oestrogen therapy can be considered as a hormonal therapy in cases with refractory menstrual migraine. An oestrogen antagonist, tamoxifen and synthetic androgen danazol have also shown benefit in some cases.<sup>30</sup>

Majority of cases require pharmacological treatment. The choice of drug is based on comorbid illness and adverse effects of medications. Acute therapy for menstrual migraine is more or less similar to non menstrual migraine; however most of the antimigraine drugs are contraindicated in pregnancy.

Among various kinds of drugs, triptans have proved to be effective in acute therapy in addition to NSAIDs.<sup>36</sup>

Parenteral magnesium has found to be useful in some cases with menstrual migraine.<sup>37</sup>

#### Migraine during pregnancy and lactation

Because of the potential teratogenicity of anti-migraine agents, all women with migraine should discuss on the issue about pregnancy with migraine treatment. The greatest risk for foetus is in the first trimester. Planned pregnancy should be advised to avoid and minimize the potential teratogenic effects of migraine medications.

### Prophylactic Treatment of Migraine

Migraine prophylaxis should be considered when the migraine attacks occur at least three or more prolonged severe attacks a month which are particularly disabling or poor response to symptomatic therapy.

#### **B-Blockers**

There was no association of an increased risk of birth defects in B-blocker usage during pregnancy. However exposure to propranolol and atenolol during pregnancy has been associated with foetal growth retardation<sup>38</sup>.

Treatment in late pregnancy and lactation may result in neonatal bradycardia, hypotension, and hypoglycaemia. Neonatal respiratory distress and apnoea have been reported in cases exposed to B-adrenoceptor blocking agents during pregnancy.<sup>39</sup>

Most B-blockers are not significantly excreted into breast milk and can be used during breastfeeding. Metoprolol or propranol are preferred drugs to atenolol or nodolol which are highly excreted into breast milk. Newborns should be closely monitored for B-receptor blockage effects such as bradycardia, hypotension and hypoglycaemia.<sup>40</sup> If prophylaxis is indicated during pregnancy or lactation, the lowest effective dose of propranolol is the first choice.

#### Tricyclic antidepressants

High-dose amitriptyline usage during pregnancy is found to be associated with limb defor maties, but causal relationship has not been established.<sup>41,42</sup> New-borns should be monitored for tachycardia, irritability, muscle spasms, and convulsion in women taking antidepressive drugs.

Amitriptyline and nortriptyline are hardly detectable in breast milk, and mother with low dose is unlikely to be associated with adverse effects in infants.<sup>43,44</sup>

#### Calcium-channel blockers, flunarizine and cinnarizine

There are no sufficient human data regarding teratogenicity or excretion into breast milk for flunarizine. Data for verapamil are limited. No association with congenital anomalies has been reported with nifedipine and verapamil.<sup>45,46</sup> However their usage in pregnancy is not advisable because of fetal bradycardia and growth retardation.<sup>47</sup>

Lisinopril can be used for migraine prophylaxis. In common with other angiotension converting enzyme inhibitors, it poses no significant foetal risk in utero during first trimester. However it causes teratogenic effects during second and third trimesters.

Captopril, enalapril and quinapril are minimally excreted in breast milk. In general, because of fetotoxicity of ACE inhibitors and angiotensin II receptor antagonist drugs, these agents should be avoided in pregnancy and lactation.<sup>48, 49</sup>

# Antiepileptics

#### Gabapentin

No harmful effects of gabapentin were recorded in early pregnancy with epilepsy. It is secreted into human milk following oral administration with a maximum dose exposure of approximately 1 mg/kg/d.<sup>50</sup>

#### Topiramate

There are reports of increased risk of oral clefts following exposure to topiramate in pregnancy. Relatively low levels are excreted into human milk<sup>51</sup>.

#### Valproic acid

Most studies involving pregnant women exposed to valporic acid have reported a high risk of foetal malformations.<sup>1, 51</sup> It is excreted in human milk in small quantities.

# New finding in migraine prophylaxis

#### Melatonin

Results from a multicentre, randomized, double-blind, placebo-controlled trial showed that efficacy of melatonin was similar to that of amitriptyline, however the adverse effect of daytime sleepiness and weight gain is less with melatonin treatment. Low level of melatonin in plasma and urine was found in patients with migraine. There is an association between melatonin level and a various type of headache including migraine attack.<sup>52</sup>

#### Acute Therapy

The following drugs should be preferred for the treatment of acute migraine attacks in pregnant women:

### Analgesics

#### Acetaminophen

Acetaminophen is the drug of choice in pregnancy. Case-control studies confirm the safety of therapeutic doses (<4 g/d) of acetaminophen during pregnancy and lactation.<sup>6</sup>

Combination analgesic, acetaminophen/aspirin/caffeine is also effective but need to be used with caution.

### NSAIDs

NSAIDs are contraindicated during the third trimester because of potential risks of causing early closure of the ductus arteriosus or pulmonary hypertension.<sup>6</sup>

# Triptans

#### Sumatriptan

There was no evidence for an increased rate of congenital malformations or other adverse effects of sumatriptan therapy in pregnancy outcomes. Study on the Sumatriptan/Naratriptan/Treximet Pregnancy Registry showed that there was no adverse outcome with sumatriptan therapy during pregnancy.<sup>53</sup> Sumatriptan can be used for severe attacks during pregnancy which do not respond to first-line drugs, and can be used during lactation without disruption to breastfeeding.

## Ergotamine and dihydroergotamine

There was no evidence of foetal deformities in use of ergotamine during pregnancy. However, ergot alkaloids are contraindicated during pregnancy because of increased uterine contraction resulting miscarriage.<sup>54</sup>

In view of potential side effects, such as weakness, vomiting and diarrhoea in nursing infants, these agents should be avoided in breast feeding.<sup>48</sup>

# Antiemetic drugs

In general the use of dopamine antagonists, metoclopramide, domperidone and phenothiazines during pregnancy has not been associated with an increased risk of malformation.<sup>55</sup> However these agents should be avoided in lactation because of adverse effects, extrapyramidal side effects with metoclopramide and cardiac arrhythmias with domperidone in infants.<sup>56, 57</sup>

# Magnesium

Parenteral magnesium is sometime useful for women with menstrual migraine or migraine during pregnancy. The rationale is that low level of magnesium levels in brain and serum have been demonstrated in some women with migraine.<sup>58,59</sup> Parenteral magnesium is an excellent choice for headache treatment in pregnant women, especially when pre-eclampsia and migraine is co-existing. Oral magnesium may be also useful in pregnancy.

### **Treatment of Peri-menopausal migraine**

Existing standard migraine therapies are equally effective in perimenopausal migraine. Low dose hormonal contraceptives in transdermal form may be considered to stabilize fluctuating oestrogen hormone level in menopausal migraine which is unresponsive to other migraine medications.<sup>60</sup>

# Conclusion

Women with migraine necessitate special attention especially during pregnancy because they are at increased risk of stroke, preeclampsia and abruption placenta. The various pharmacologic drugs used for migraine may also increase the incidence of foetal malformations.

Non-pharmacological therapy may alleviate migraine symptoms but majority need anti migraine agents. For those who have at least 3 or more severe prolonged attacks a month, migraine prophylaxis should be considered. B blockers are effective for women with migraine without aura. Amitriptyline is useful for prophylaxis during first and second trimester as well as during lactation.

For acute attacks of migraine, aspirin, paracetamol and NSAID, especially ibuprofen are useful in first and second trimesters, however these agents should be avoided during third trimester of pregnancy. Triptans are also useful in first trimester. Among the various type of triptan, sumatriptan is the first choice of treatment for acute attack. As a hormonal therapy, oestrogen therapy may be considered in refractory menstrual migraine. Shortterm HRT, especially transdermal form may be beneficial in cases with menopausal migraine.

# **Further Research**

Further research is needed to explore the pathophysiological changes concerning neurotransmitters in brain at cellular level. Novel drugs targeted on these changes must be innovated.

### **Data Sources**

All the relevant articles from Medline, PubMed and Medscape were searched using the key terms migraine, women, prophylaxis and treatment. National Guideline Clearinghouse was searched for related guidelines.

Declaration of interest: The authors have no conflicts of interest.

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