Women and Migraine: The Hormonal Link

**Annual Review of Family Medicine**
April 12, 2010

**Norma Jo Waxman MD**
Associate Professor of Family and Community Medicine
Faculty in the Bixby Center for Global Reproductive Health
University of California San Francisco
njwaxman@fcm.ucsf.edu

---

**Learning Objectives**

- Recognize migraine with and without aura, menstrually related migraine, and true menstrual migraine
- Utilize behavioral and pharmacologic options for acute and prophylactic management of migraine
- Understand when hormonal medication is helpful and safe for all ages of women with migraine
- Decrease incidence of chronic daily headache in your practice

---

**Why Care About Migraine?**

- Very Common neurologic disorder
  - Underrecognized
  - Undertreated
- Produces severe disability
- Overuse of any drug may lead to chronic daily HAs

---

**Faculty Disclosure**

No pharmaceutical support or commercial disclosures

Member of ARHP expert advisory committee on Hormonal Migraines and developed slide set. Many used in this presentation

---

**References**

Migraine in USA

- 30 million migraine sufferers
- 1 in 10 persons a migraineur
- 1 of 4 households include a migraineur
- 9th leading disability, more common than diabetes or asthma
  - 30% of migraineurs have 3+ attacks/mo.
  - 75% have reduced ability to function
  - 50% are severely impaired


Epidemiology of Migraine in Women

Women are affected 3x more than men

- 20 million women in USA
- 40% of women in their lifetime
  - Before puberty: equally prevalent in both sexes
  - After puberty: 3x more women than men
  - Peaks in midlife
  - ↓ after menopause


ICHDA Diagnostic Criteria for Migraine Without Aura

- At least 5 attacks with:
- Headache lasts 4–72 hours w/o treatment or without successful treatment
- At least 2 of the following four symptoms:
  - Unilateral pain (60%)
  - Throbbing (70%)
  - Aggravation by movement
  - Moderate to severe pain

ICHDA – International Classification of Headache Disorders

IHS Diagnostic Criteria for Migraine Without Aura (*cont’d*)

- And at least 1 of the following 2 symptoms:
  - Nausea and/or vomiting
  - Photophobia and/or phonophobia

- Not attributed to organic disease

ICHD Diagnostic Criteria for Migraine with Aura

- At least 2 attacks with
- At least 1 fully reversible symptom w/o motor
  - Visual (flickering lights, zigzags, spots or lines, and/or loss of vision) + and/or
  - Sensory (“pins and needles” and/or numbness) + and/or
  - Dysphasic speech

Adapted from IHS, Cephalalgia, 2004.

more...

IHS Diagnostic Criteria for Migraine with Aura (cont’d)

- Symptoms of aura develop gradually over >5 min or different symptoms occur in succession over >5 min
- Each symptom last >5 and <60 min
- Migraine begins with aura or within <60 min
- Symptoms are fully reversible
- No organic disease

Adapted from IHS, Cephalalgia, 2004.

Prevalence of Migraine by Age and Sex


Headaches and the Menstrual Cycle

**Menstrual Migraines Subtypes (ICHD-2)**

**Menstrually Related Migraine (MRM)**
- Attacks fulfill criteria for 1.1 Migraine without aura
- Attacks occur days 1 ± 2 (i.e., days -2 to +3) of menstruation in at least 2 out of 3 menstrual cycles and additionally at other times of the cycle
- ~46% of women with migraine

**Pure Menstrual Migraine (MM)**
- Attacks fulfill criteria for 1.1 Migraine without aura
- Attacks occur days 1 ± 2 (i.e., days -2 to +3) of menstruation in at least 2/3 cycles, and at no other time of the cycle
- ~14% of women with migraine

---

**Distribution of Migraine Types in Women**

- 40% non-menstrual migraine
- 60% menstrual migraine
  - MRM comprises the majority of MM (46% of 60%)

---

**Non-Hormonal Migraine Triggers**

- Hunger
- Certain Foods
- Dehydration
- Sleep
- Head and neck pains
- Emotional
- Environmental: smoke, bright lights, change in weather
- Concomitant disease
- Sex

---

**Menstrual Migraines**

- Compared with attacks at other times of the cycle, menstrual attacks are:
  - More disabling
  - Longer in duration
  - Less responsive to acute treatment
  - More likely to relapse

---


Hormonal Migraine Triggers

- Estrogen withdrawal, or change in level
  - Menstruation
  - Placebo days with combined hormonal contraceptives
  - Pregnancy
  - Peri-menopause
  - Hormone replacement therapy

Case 1: Sarah

New Patient Visit

- 24-year-old non-smoker
- Sexually active
- On intake: checks off "headaches," which she says are worse with her periods
- Presents for contraception

Does Sarah have migraine?...

Accurate diagnosis of migraine aura is essential for the safe prescribing of estrogen-containing OCPs.

Sarah has migraine without aura. She has no other risk factors for stroke.

OCP = oral contraceptive pills

Is Sarah eligible for estrogen-containing OCPs?

A. Yes
B. No
Case 1: Sarah

- Is Sarah eligible for estrogen-containing contraceptives? Might she opt for a patch or ring?

A) Yes: Low-dose estrogen contraception can be used in women under age 35 who have migraine without aura and no other risk factors for stroke.

B) No: OCPs should never be used in women who have migraine.

WHO: Headaches and CHC

<table>
<thead>
<tr>
<th>Initiate</th>
<th>Continue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-migrainous (mild or severe)</td>
<td>1</td>
</tr>
<tr>
<td>Migraine</td>
<td></td>
</tr>
<tr>
<td>(i) without focal neurologic symptoms</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 35</td>
<td>2</td>
</tr>
<tr>
<td>Age &gt; 35</td>
<td>3</td>
</tr>
<tr>
<td>(ii) with focal neurologic symptoms</td>
<td>4</td>
</tr>
<tr>
<td>(at any age)</td>
<td></td>
</tr>
</tbody>
</table>

Prodrome = photo/phonophobia, N/V – These are not focal symptoms

Focal symptoms = vision changes, numbness, parasthesias

http://www.who.int/reproductive-health/publications/RHR_00_2_medical_eligibility_criteria_3rd/

Treatment of Migraines

- Education and behavior modification
  - Identify and avoid or modify triggers

- Acute treatment

- Prophylactic treatment
  - Short-term
  - Long-term

Treatment of Migraines

- **Triptans** more effective than NSAIDs and combination analgesics—warn about SEs

- NSAIDS can act synergistically with Triptans

- Phenothiazines, PO or PR, great for nausea & pain

- Think non-oral meds with nausea & vomiting

- Sleep can abolishes headache
### Options for Acute Therapy
- Aspirin
- Ibuprofen
- Naproxen sodium
- Combination Analgesics
  - Acetaminophen, aspirin and caffeine
- Triptans
- Phenothiazines

### Rescue or Emergency Treatment of Migraine
- When acute tx fails
- When H/A returns in <24 hrs or continues for days
- IV/IM phenothiazines in addition to DHE or a triptan work better than narcotics.

### Prophylaxis of Migraines
- Consider prophylaxis if acute meds used > 4x/mo, rescue meds > 1x/mo, or headaches are functionally limiting
- Start prophylaxis at low dose and titrate up over 2–3 months
- TCAs are effective independent of their antidepressant effect
- Limited studies show biofeedback, relaxation training, spinal manipulation and physical therapy may be helpful

### Medications for Prophylaxis
- Consider hx, co-morbidities and hormonal state
  - TCAs- Amitrip best
  - SNRIs (more effective then SSRIs)
  - Beta- blockers-
    - Propranolol most studied and successful- Nadolol and Timolol too
  - Valproate, Topiramate, Gabapentin and other “anti-convulsants” and “mood stabilizers”
  - Botox
  - Verapamil and CCB- less effective
  - Hormonal Tx
Preventive Options with Non-pharmacologic Modalities

Supplements

- Magnesium
- Vitamin B2 - riboflavin
- Feverfew
- Butterbur (Petadolex)
- Coenzyme Q10
- Omega-3 Fatty Acids
- Isoflavones

Chelated magnesium at 400-600 mg/d for 3-4 months works as prophylaxis (best in pt. w/ aura or perimenstrual migraine, and those not responding to triptans). Riboflavin, 400mg/d for 3 months decreases migraine frequency.

Red Flags

- Headaches begin after age 50
- Very sudden onset of Headache
- First or worst
- Change in frequency or severity
- Immunosuppression
- Fever, stiff neck, rash, trauma
- Focal neurologic symptoms or signs
- Papilledema

Case 1: Sarah

Recommended Approach

- Migraine diary
- Counseling about migraine triggers and non-pharmacologic treatment options
- Her choice of hormonal / non-hormonal contraception
- Acute treatment with triptan
- Schedule 2-3 mo f/u to review diary
Case 1: Sarah
Return Visit

- Headache diary confirms menstrual related migraine
  - 2–3 attacks/mo. without aura
  - Severe attack during pill-free week

What do you do next?...

Options for Pharmacologic Treatment for MRM

Rescue/Emergency treatments
- IM/IV phenothiazines or DHE

Prophylactic perimenstrual treatments
- NSAIDs
- Supplemental estrogen
- Triptans
- Extended cycle combined hormonal contraceptives

Prophylactic Treatments for MM and MRM with Continuous hormonal therapy

Continuous combined contraceptives
- Dedicated product
- Monophasic product throw away placebo
- Continuous cycling with ring

Estrogen back in hormone-free interval
- Mircette
- Yaz
- Supplemental estrogen

Migraine, OCPs, and Stroke

- 6 per 100,000 ♀ / year – healthy
- 12 per 100,000 ♀ / year – migraine
- 18 per 100,000 ♀ / year – migraine with aura
- 12 per 100,000 ♀ / year – healthy and COC
- 19 per 100,000 ♀ / year – migraine and COC
- 30 per 100,000 ♀ / year – migraine with aura and COC
- 34 per 100,000 ♀ / year – stroke in pregnancy

Attributable risk: 7-19 per 100,000 women per year ~ 4000 / year

So, What about estrogen containing contraception in women with Migraine?
- IHS: low-dose estrogen in women with simple visual aura
- ACOG: progestin only, intrauterine or barrier contraception
- WHO: absolute contraindication in all women with aura
Case 2: Pam

- 35-year-old woman
- 6th week of pregnancy
- Menstrual migraine diagnosed 10 years ago
- Migraine more frequent and severe since she became pregnant

Migraine and MRM in Pregnancy

- 60% – 70% of migraineurs improve during pregnancy

- Non-pharmacologic treatment is preferred
  - Biofeedback
  - Relaxation therapy
  - Cognitive-behavioral therapy
  - Magnesium


Migraine Drug Use During Pregnancy and Lactation (Analgesics and Ergots)

<table>
<thead>
<tr>
<th>Drug</th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Codeine</td>
<td>(Y)</td>
<td>(Y)</td>
<td>(Y)</td>
<td>Y</td>
</tr>
<tr>
<td>Aspirin</td>
<td>(Y)</td>
<td>(Y)</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Diclofen酸</td>
<td>(Y)</td>
<td>(Y)</td>
<td>Avoid</td>
<td>Y</td>
</tr>
<tr>
<td>Naproxen</td>
<td>(Y)</td>
<td>(Y)</td>
<td>Avoid</td>
<td>Y</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
</tbody>
</table>

Y = no evidence of harm
(Y) = data suggest unlikely to cause harm
? = limited data but probably safe
CI = contraindicated
ID = insufficient data
* = for emergency treatment of migraine not responding to standard measures

Case 2: Pam Treatment and Outcome

- **Reassurance**
  - Migraine may improve by the 2nd trimester, particularly in women w/ history of menstrual migraine
  - No evidence migraine will affect pregnancy outcome

- **Acute**
  - Acetaminophen, NSAIDS, Triptans ??? (1-2nd trimester- may be safe- need more studies)

- **Prophylactic**
  - If possible, delay treatment until 2nd trimester
Case 2: Pam
Treatment and Outcome (cont’d)

- **Propranolol** is safe and effective and can be used postpartum and during lactation (FDA C)
  - Use lowest effective dose
  - Stop 2 to 3 days before delivery
  - Manage with neurologist or headache specialist
- **Amitriptyline** is another option
  - (FDA C)

Case 3: Hannah

- 52-year-old woman
- Presents with headache
- 5-year history of menstrual migraine and occasional attacks of migraine with aura
- Hot flashes, mood swings
- Asks about hormone therapy

Menstrual Migraine and Hormone Therapy (HT)

- Lowest and Non oral routes are best
- Evaluate risk factors for stroke and CAD
- Migraine with aura is **not** a contraindication to HT in low risk women (no RCTs, expert opinion)
- If aura 1st appears after start of HT, reduce estrogen and consider work up for TIA


Case 3: Hannah

- Acute treatment with NSAIDS & triptans
- Low-dose non-oral estradiol AND continuous progestin (if needed)
- Hannah’s migraine attacks increase when HT is initiated but improve with continued use
- Fluoxetine & venlafaxime useful migraine prophylaxis and treat hot flashes
Chronic Daily Headache (CDH)

- **Diagnostic Criteria:** Headache 15 or more days/month for at least 6 months
- Preventable with accurate medication history
- Speaks to early use of prophylaxis
- Depression, anxiety and drug abuse may complicate presentation

Chronic Daily Headache (CDH)

- AKA: rebound headache, chronic tension-type, medication induced, transformed migraine
- CDH caused by **overuse of acute** meds
- **Unrecognized epidemic:** majority of referrals to headache clinics
- Disabling and expensive

Summary: Behavioral and Lifestyle Modifications

- Avoid dietary, emotional, and environmental triggers
- Eat regular, healthful meals
- Get the right amount of sleep
- Get regular exercise
- Learn stress management techniques

Chronic Daily Headache (CDH)

- Taper off acute medications
- Overuse of NSAIDs, tylenol, narcotics typical
- May require hospitalization
- 6 RCTs showed sig improvement w/ Amitriptyline
- The longer one has CDH, the harder it is to treat
- Steroids may be helpful during taper
Take-Home Points

- Migraine is a neurological illness caused by abnormality in brain chemistry
- A range of behavioral and drug options exist for the management of severe migraine
- A substantial proportion of women with migraine experience increased incidence around onset of menses
- Short-term prevention is the best approach for these women if they have regular menses