PainWeek

La Femme Migraineur:
What Does Estrogen Have to Do with Migraine?

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Disclosures

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Nothing to disclose

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Learning Objectives

- Explain to patients the role that estrogen plays in migraine over the lifecycle
- Diagnose menstrually related migraine
- Counsel patients the risks and benefits of exogenous estrogen use to treat migraine

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"Among all the factors involved in gender differences, sex hormones may be the most **impotent**"

W. Li et al. / Journal of Clinical Neuroscience 50 (2018) 165–171

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The "Top 10" Migraine Precipitating Factors

#5 – Hormones

Experienced by 50-60% of

Female migraine pts

Peroutka, S.J. Curr Pain Headache Rep (2014) 18: 454. https://doi-org.laneproxy.stanford.edu/10.1007/s11916-014-0454-z

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Summary Slide

- Estrogen can modulate migraine over the female lifecycle
  - Menstrually related migraine
  - Estrogen withdrawal or exogenous estrogen induced headache
  - Migraine and pregnancy
  - Migraine and breastfeeding
  - Migraine and menopause
- Estrogen can modulate peripheral and central systems that impact our perception and ability to modulate pain
- Treatment depends on proper diagnosis

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The Lifecycle and Sex

- Pre-puberty prevalence: 3-10% - no gender difference
- Puberty - migraine becomes 2–3 times more common in women than in men
- After puberty -50% of female migraine attacks thought to be menstrually related

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Cairns BE et al. Maturitas 63:292-296. 2009
Silberstein SD Rev Neurol (Paris) 156(Suppl 4):4S30–4S41. 2000

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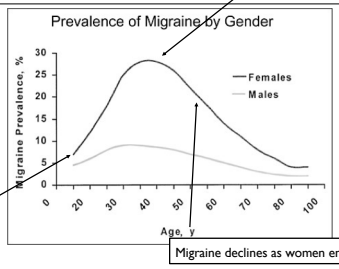
Migraine Lifecycle

Migraine peaks age 35-45 for women with 25-30% of females affected vs 8% males



Stewart WF, Lipton RB, Celentano DD,Reed ML. 1992. *JAMA* **267**:64–69.

Boys and girls have equal rates of migraine until age 9

Migraine declines as women enter menopause

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Menstrual Migraine

- Most frequently occurs in the second decade of life around the onset of menarche
- Typically without aura
- Common - occurring in 60% of women who have migraine attacks
- A much smaller percentage, 7 to 35% of women experience migraine attacks that may occur before, during, or after menstruation
- Prevalence peaks around age 40, declines as menopause approaches

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Todd C at al. Current Neurology and Neuroscience Reports (2018) 18: 42

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ICHD3 – Menstrual Migraine

Menstrually Related Migraine (MRM)

- Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura* and criterion B 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.

Pure Menstrual Migraine (PMM)

- Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura* and criterion B 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.
- https://ichd-3.org/

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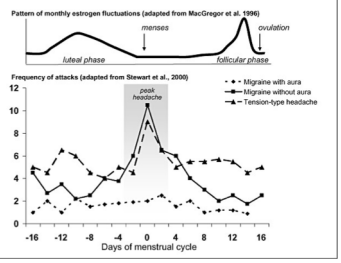
Relationship of Headache to Circulating Estrogen



Martin VT(Headache 2008;48:S124-S130)

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Estrogen withdrawal hypothesis

- Estrogen withdrawal hypothesis - developed by Somerville and colleagues in 1972, postulates that attacks of menstrual migraine are triggered by the decrease in estrogen levels preceding menstruation

Somerville BW. Neurology. 1972 Apr;22(4):355-65.

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Diagnosis

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Treatment

- Why not give everyone estrogen?

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Exogenous hormone induced headache

- Headache attributed to long-term use of non-headache medication
- Headache developing as an adverse event during hormone therapy (previously coded as *Headache attributed to exogenous hormone*).
  - Regular use of exogenous hormones can be associated with an increase in frequency or new development of migraine-like or other headache.
  - When a pre-existing headache with the characteristics of a primary headache disorder becomes *chronic*, or is made *significantly worse* (usually meaning a two-fold or greater increase in frequency and/or severity), in close temporal relation to regular use of exogenous hormones

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Exogenous estrogen headaches

- **Estrogen Withdrawal Headache**
- Headache or migraine developing within 5 days after daily consumption of exogenous estrogen for 3 weeks or longer, which has been interrupted (usually during the pill-free interval of combined oral contraception or following a course of replacement or supplementary estrogen). It resolves spontaneously within 3 days in the absence of further consumption.

Headache or migraine
Daily use of exogenous estrogen for ≥3 weeks, which has been interrupted
Evidence of causation demonstrated by both of the following:
- headache or migraine has developed within 5 days after the last use of estrogen
- headache or migraine has resolved within 3 days of its onset

https://ichd-3.org/

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Sacco et al. The Journal of Headache and Pain (2018) 19:76
https://doi.org/10.1186/s10194-018-0896-5

The Journal of Headache and Pain

CONSENSUS ARTICLE Open Access

Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH)

Simona Sacco[1*], Gabriele S. Merki-Feld[2], Karen Lehrmann Ægidius[3], Johannes Bitzer[4], Marianne Canonico[5], Andreas R. Gantenbein[6], Tobias Kurth[7], Christian Lampl[8], Øyvind Lidegaard[9], E. Anne MacGregor[10,11], Antoinette MaassenVanDenBrink[12], Dimos-Dimitrios Mitsikostas[13], Rossella Elena Nappi[14,15], George Ntaios[16], Koen Paemeleire[18], Per Morten Sandset[19], Gisela Marie Terwindt[20], Kjersti Grøtta Vetvik[21], Paolo Martelletti[22] and on behalf of the European Headache Federation (EHF), the European Society of Contraception and Reproductive Health (ESCRH)

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To use estrogen or not to use estrogen: MRM

- Extended CHC for women with MRM: Suggested Low/Weak
  - who require CHC for medical/contraceptive
  - who would prefer CHC to other preventive options or have failed other preventive options
  - Vaginal ring is also an option
  - For pure supplementation during the week of menses, transdermal supplementation with estradiol gel over estradiol patch is recommended

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To use estrogen or not to use estrogen: Migraine (not related to menses)

CHC Vaginal Ring or Extended regimen of pills or patches
For women with migraine, non menstrually mediated, who require treatment for contraceptive or medical reasons
Low/Weak

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To use estrogen or not to use estrogen: MwA

- Migraine with aura (MwA) does carry an increased risk of stroke compared to migraine without aura. This risk was demonstrated primarily in older studies with women receiving significantly higher doses of estrogen than used today
- Emerging evidence from clinical practice however suggests that there is lower risk in prescribing the current low-estrogen formulations to patients with MwA assuming they have a low vascular risk profile (nonsmokers, no cardiovascular risk factors)

Sacco S, Ricci S, Degan D, Carolei A. *J Headache Pain*. 2012;13(3):177-189
de Falco FA, de Falco A. *Neurol Sci*. 2015;36 Suppl 1:57-60

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To use estrogen or not to use estrogen: MwA

- In women for whom estrogen-containing contraceptives are contraindicated, a progesterone-only pill can be considered and the EHF/ESCRH consensus statement suggests desogestrel (the only progestin studied) for MwA patients who require treatment for contraception or medical reasons, or who have failed other preventive options

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Is the migraine only due to the drop in estrogen?

- End –menses migraines:
- In one retrospective study with 85 female patients with menstrual migraine, 35.3% reported migraine headache onset by the end of menstruation, which is days after the estrogen drop. The authors hypothesize that this type of migraine headache is not related to hormonal changes but most probably to transient anemia due to blood loss (Calhoun A, Headache. 2017 Jan;57(1):17-20)
- A Turkish study noted an increased prevalence of iron deficiency anemia in all migraine patients as compared to healthy controls and significant association between migraine and iron deficiency anemia in the menstrual migraine subgroup. (Gur-Ozmen S, Karahan-Ozcan R. *Pain Med.* 2016;17(3):596-605)

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Estrogen and Pain

- Estrogen has been shown to impact the system response at the level of
  - –Dura
  - –Peripheral nerve
  - –Trigeminal ganglion
  - –Trigeminal nucleus
  - –Thalamus
  - –Cortical systems
  - –Descending modulatory systems

Borsook et al. Neurobiology of Disease 68 (2014) 200–214

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Estrogen and Pain

Fluctuations in hormonal levels have been shown to influence
- Sensitivity to thermal pain in healthy women
- Experimental muscle pain in women with dysmenorrhea
- Pain intensity, unpleasantness and functional brain activity in response to noxious stimuli

Borsook et al. Neurobiology of Disease 68 (2014) 200–214

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Estrogen and Pain

- Evidence of changes in the brain across the menstrual cycle in females
- gray matter volume peaks were found during ovulation compared to follicular and luteal cycle phases
- Gray matter and white matter fluctuations in brain regions related to emotion and cognition across the menstrual cycle
- women using a hormonal birth control method have greater gray matter volumes in prefrontal cortices, pre- and postcentral gyri, parahippocampal/fusiform gyri, and temporal regions as compared to naturally cycling women

Borsook et al. Neurobiology of Disease 68 (2014) 200–214

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Downstream effects of estrogen

- Obese women appear to have more than a twofold risk of episodic and chronic migraine, probably due to the pathological estrogen production in adipose tissue
- Estrogen modulates serotonergic neurotransmission, by increasing the expression of the tryptophan hydroxylase and decreasing the expression of the serotonin reuptake transporter
- Estrogen also activates the endogenous opioidergic system, which has an analgesic effect on persistent, inflammatory pain
- Furthermore, estrogen induces vascular changes by modulating vasodilation and suppressing vascular inflammatory response

Horev et al.2005. Headache 45; Fava et al 2014. Eur J Neurol 21; Gupta S et al 2011. Headache 51; Warnock et al 2017.Pharmacotherapy 37; Krause DN et al 1985.J Appl Physiolo;; Miller M et al. 2008 Pharmacol Rev 60.

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Treatment

1. Lifestyle
2. Is prevention warranted?
3. Mini-prophylaxis
4. Rescue

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Is prevention warranted

- > 4 days a month

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Mini Prophylaxis

Non-hormonal options:

- perimenstrual use of NSAIDs
  - –naproxen sodium (550 mg BID) may be used effectively 2– 4 days prior to the MM and continued through day 3 of menstrual flow
- Modified triptans regimens including sumatriptan (25 mg TID), naratriptan (1 mg BID), and frovatriptan (2.5 mg BID) , started 2 days prior to the onset of MM and continued for a total of 3–5 days.
- Standard prophylactic medications may be used for 5–7 days prior to the onset of menses and continued through to the end of the vulnerable time period for migraine – this can be a transient increase in the preventive currently used

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Mini Prophylaxis

Hormonal options:

- transdermal supplementation with estradiol gel is recommended over an estradiol patch during the week of menses

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Acute / Rescue

- For acute medications, triptans with the possible addition of NSAIDs and/or antiemetic is a good first choice

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Headache and Pregnancy

- 1st Trimester: Rise in estrogen
- 2nd/3rd Trimester: Estrogen stability
- 50-75% of women experience improvement in headache during pregnancy
- Pay attention to women with severe maternal migraines

  2 studies showing increase in adverse delivery outcomes in women seeking treatment for acute migraine (Grossman TB et al, Headache 2017; Chen HM et al Cephalalgia 2010)

- look for red flags

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It's a new headache – RED FLAGS

- **Sudden** onset headache reaching maximal intensity in <1 minute
- **New** onset of severe headache or significant changes in headaches
- **Worsening** headache with fever, meningism
- Headache **triggered by cough, valsalva, sneezing, or exercise** suggestive of raised intracranial pressure (drowsiness, diplopia, papilloedema)
- **Orthostatic** headache
- New onset **focal neurological deficit, cognitive dysfunction, or seizures**
- Recent head or neck **trauma**
- Headache with impaired consciousness or personality changes
- Headache with unusual aura (duration >1 hour or including motor weakness)
- **Progressive** headache worsening over weeks or months
- Visual disturbance or visual field defect
- Symptoms suggestive of giant cell arteritis or glaucoma

Jarvis S *BMJ* 2018;360:k80

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Secondary causes of headache in pregnancy

- Hypertension or pre-eclampsia
- Idiopathic intracranial hypertension
- Subarachnoid hemorrhage
- Cerebral venous thrombosis
- Meningitis
- Reversible cerebral vasoconstriction syndrome
- Space-occupying lesions
- Posterior reversible encephalopathy syndrome
- Pituitary diseases (pituitary adenoma, apoplexy, acute Sheehan's syndrome, lymphocytic hypophysitis)
- Other causes of headache—Cervicogenic headaches, medication overuse headaches (patients taking abortive treatment >2-3 times a week), caffeine withdrawal headache, giant cell arteritis (>50 years old), carotid or vertebral dissection, pheochromocytoma, temporomandibular joint pain, carbon monoxide poisoning, post-epidural puncture headache

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Jarvis S *BMJ* 2018;360:k80

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Strategies for treatment of migraine in pregnancy

- Hydrate with a minimum of 2 liters of water per day
- Avoid skipping meals
- Reduce caffeine intake but avoid sudden withdrawal
- Sleep hygiene—Avoid bright lights and mobile phone use; have appropriate amount of sleep (7-8 hours a night)
- Regular exercise
- Behavioral medicine strategies—Such as biofeedback and relaxation therapy, non-invasive stimulation devices (transcutaneous supraorbital nerve stimulation)

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Jarvis S *BMJ* 2018;360:k80

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Migraine Prophylaxis

- Aspirin 75 mg once a day (Rolnik DL, Wright D, Poon LC, etal . Aspirin versus placebo in pregnancies at high risk of preeclampsia. N Engl J Med 2017;377:613-22)
- β Blockers such as low dose propanolol (10-40 mg three times a day)
- Verapmail (less evidence but used in cluster and pregnancy)
- Low dose tricyclic antidepressants such as amitriptyline 10-25 mg taken at night can be considered
- Do not use topiramate and sodium valproate as they are teratogenic

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Jarvis S
BMJ 2018;360:k80

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Treatment

- First line analgesia
  - acetaminophen
  - avoid opiates
  - avoid NSAIDs
- Antiemetics such as prochlorperazine, cyclizine (first line), domperidone, ondansetron, and metoclopramide are safe to use in pregnancy. Avoid long term use of metoclopramide because of its extrapyramidal side effects
- Greater occipital nerve block can alleviate pain and reduce the number of headache days and medication consumption
- For severe intractable migraine, consider serotonin receptor agonists such as sumatriptan, which has not been shown to be associated with adverse outcome
- Avoid ergotamines in pregnancy

Jarvis S *BMJ* 2018;360:k80

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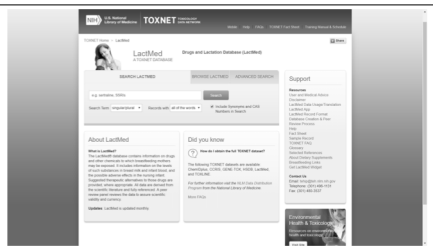
Migraine and Breastfeeding



https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

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Migraine and Menopause

- Women enter perimenopause in their mid-forties or earlier – reach menopause by age 55
- Erratic hormone levels can make headaches unpredictable during menopause
- makes this population vulnerable to MOH
- HRT can be considered but may worsen migraine
- Gabapentin, venlafaxine, natural supplements

Todd C. et al. Current Neurology and Neuroscience Reports (2018) 18: 42

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Summary

- Estrogen can modulate migraine over the female lifecycle
  - Menstrually related migraine
  - Estrogen withdrawal or exogenous estrogen induced headache
  - Migraine and pregnancy
  - Migraine and breastfeeding
  - Migraine and menopause
- Estrogen can modulate peripheral and central systems that impact our perception and ability to modulate pain
- Treatment depends on proper diagnosis

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