Headaches and Hormones

Carolyn Bernstein MD FAHS

Lavine Family Distinguished Chair in Neurology. Brigham and Women's Hospital

Associate Professor of Neurology, Harvard Medical School

John Graham Headache Center, BWFH Hospital

Osher Clinical Center for Integrative Medicine, BWH

- Dr. Bernstein consults for Percept and receives research support from Teva.

- There are huge research gaps around migraine and hormones
- Opportunity to brainstorm about studies going forward.

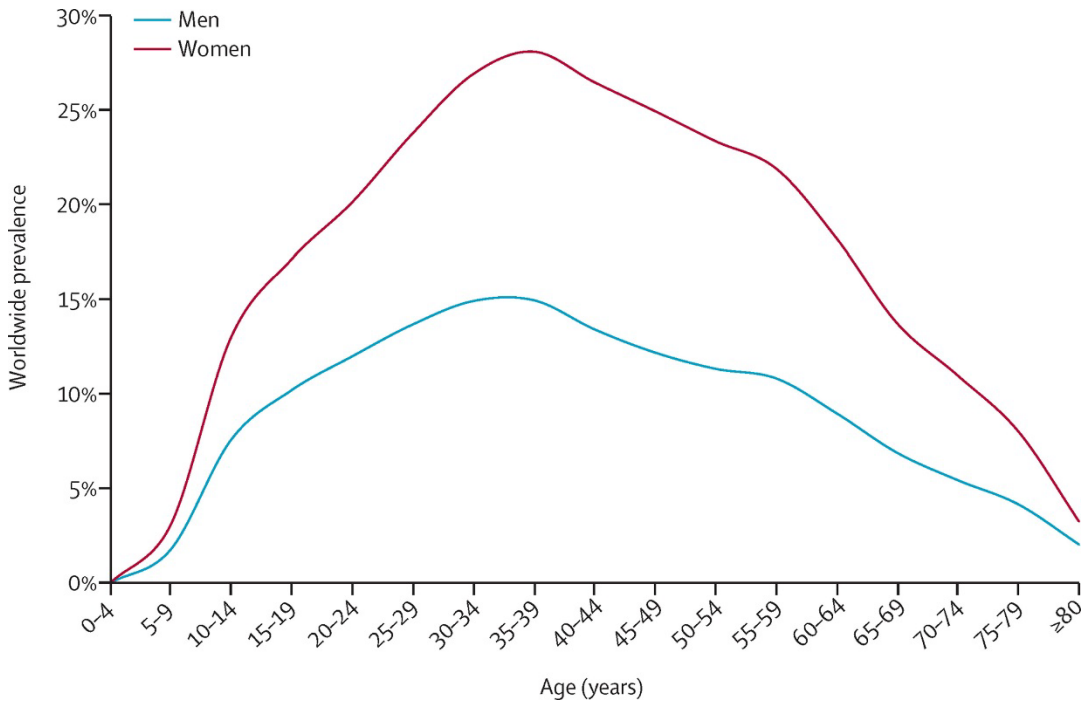
Lecture Objectives

UNDERSTAND HOW HORMONES AFFECT MIGRAINE OVER A WOMAN'S LIFE

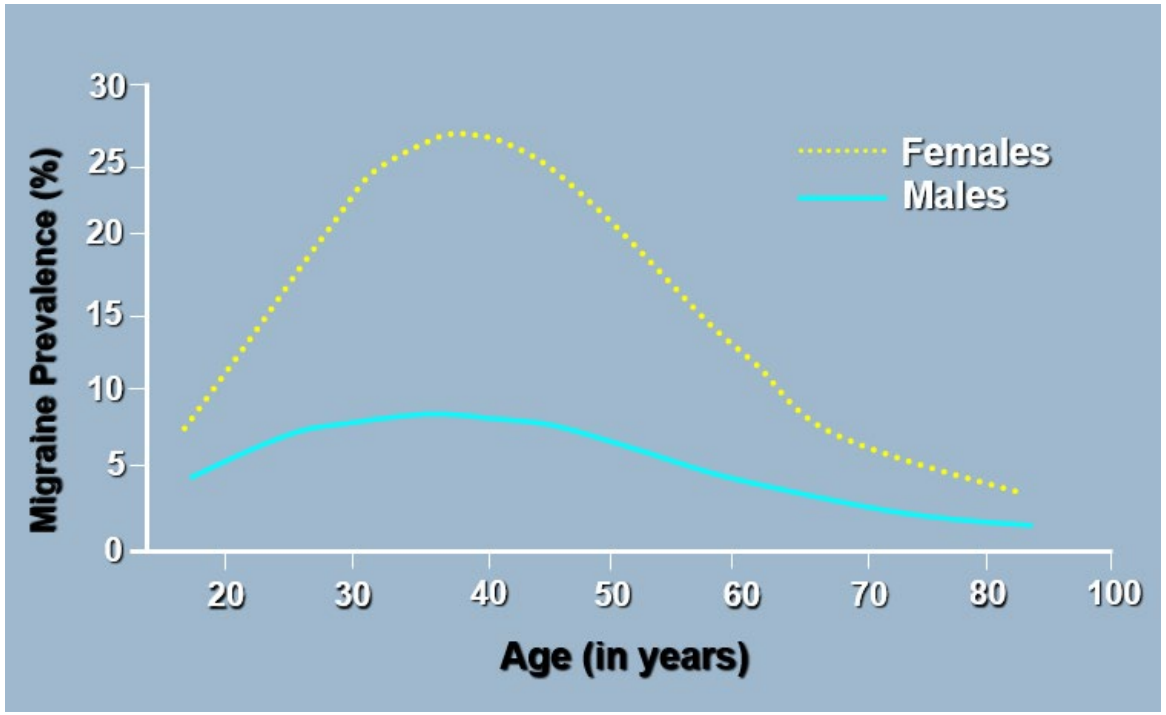
UNDERSTAND CONCERNS AROUND ADDING EXOGENOUS HORMONES FOR WOMEN WITH MIGRAINE

UNDERSTAND TREATMENT OPTIONS, MEDICATION AND INTEGRATIVE, FOR WOMEN WITH MIGRAINE

Prevalence of migraine



Worldwide



United States

Global Burden of Disease Study 2015 (GBD 2015), Institute for Health Metrics and Evaluation, Seattle, WA (2016); Lipton R, Headache, 41 (2001)

Migraine Definitions ICHD 3Beta Criteria

- Migraine without Aura
- unilateral
- Throbbing
- Moderate to severe intensity
- Nausea or vomiting
- Photo and phonophobia
- Lasts 4-72 hours
- At least five events

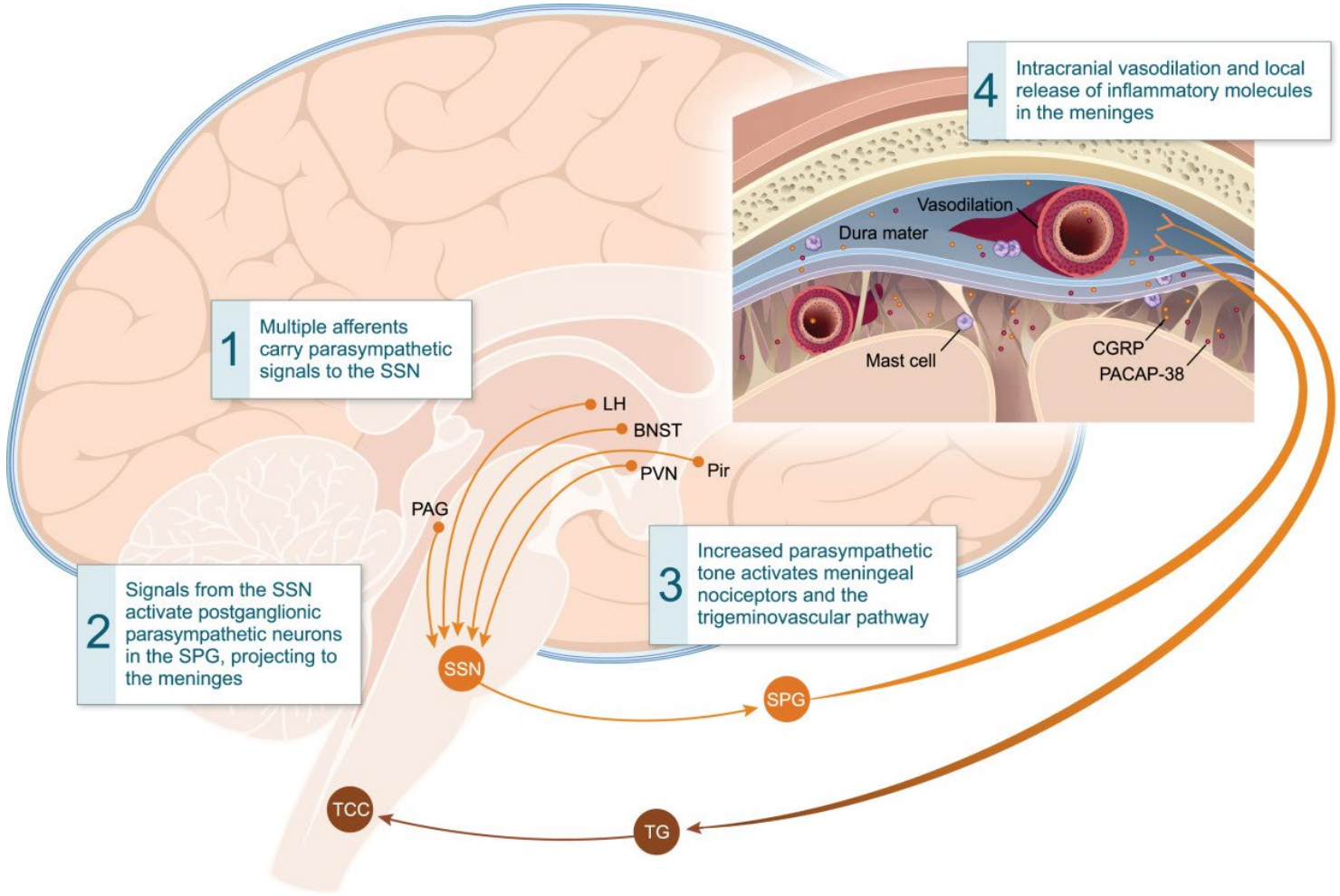
- Migraine with Aura
- 5-60 min preceding event
- Visual/sensory/language
- Lasts 4 to 72 hours
- 2 events
- Otherwise same

Why does aura matter? Migraine and stroke risk

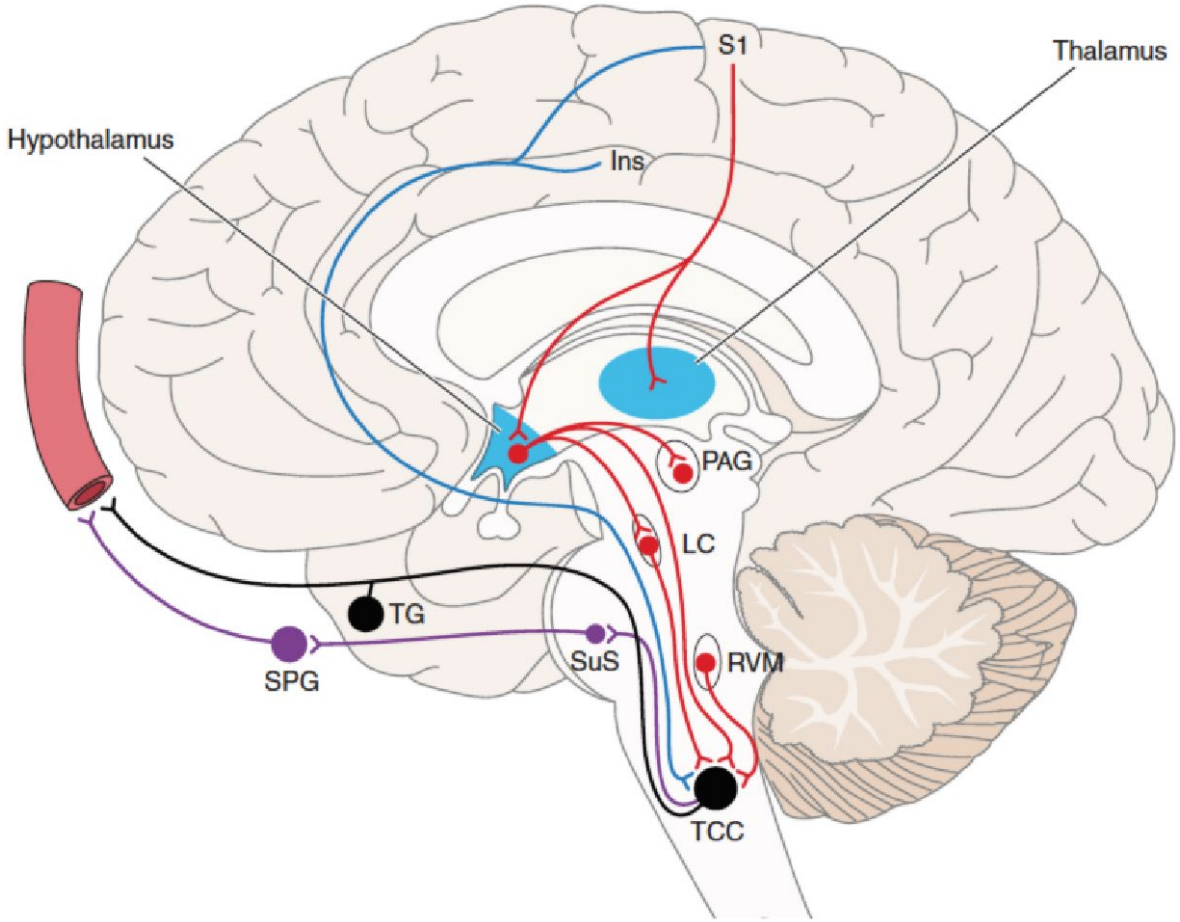
- Relative risk for ischemic stroke is about double in women with migraine with aura
  - Risk for hemorrhagic stroke likely also increased
- Risk greatest for women under 45 and without other cardiovascular risk factors
- Increased frequency of attacks and recent onset associated with increased risk

Sacco and Kurth Current Cariology REP 2014

A Phase-by-Phase Review of Migraine Pathophysiology



Headache: The Journal of Head and Face Pain, Volume: 58, Issue: S1, Pages: 4-16, First published: 26 April 2018, DOI: (10.1111/head.13300)



Peter Goadsby et al., Physiol Rev 97: 553–622, 2017.

Why do women have more migraine?

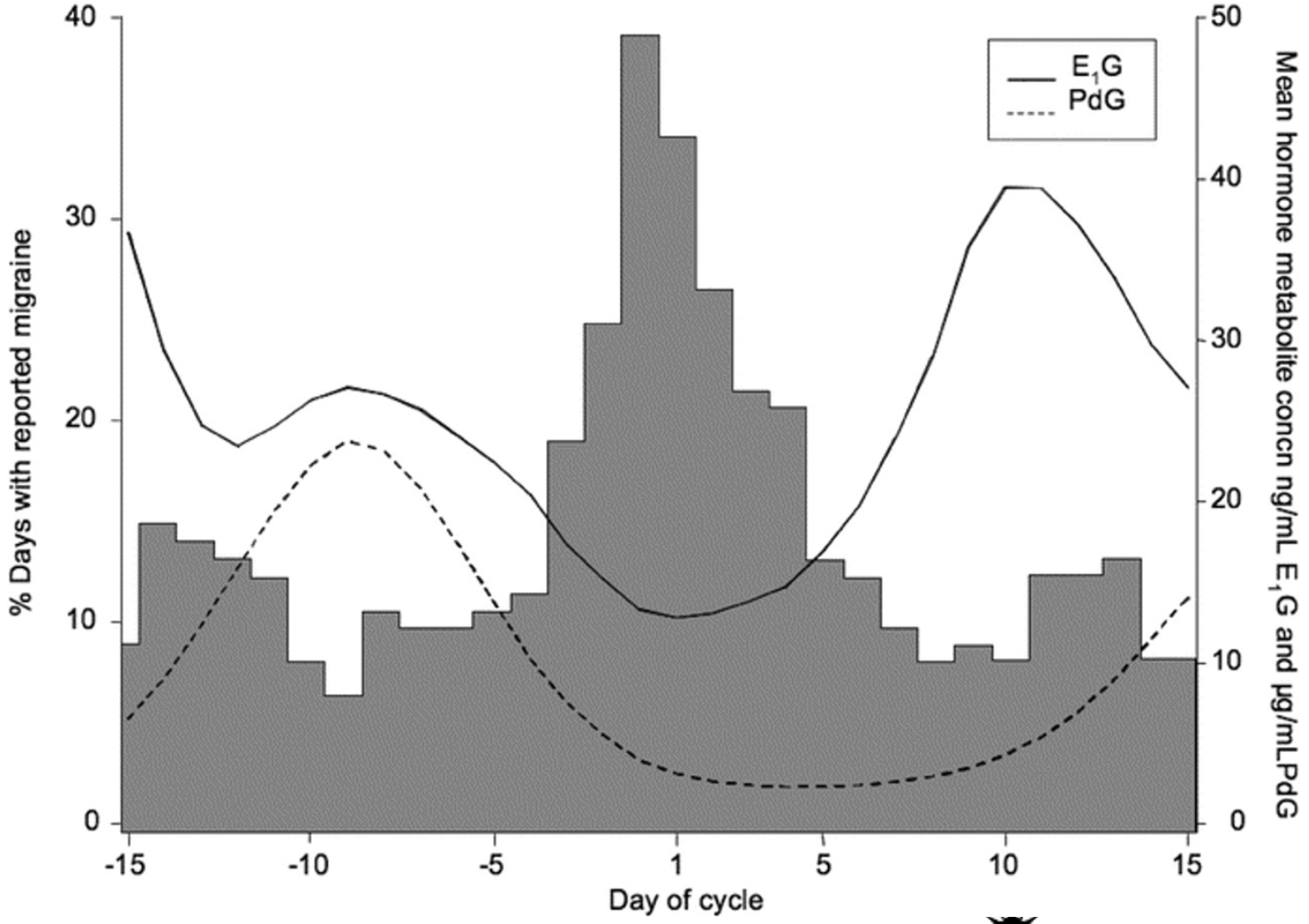
Hormonal factors may account for differences.

2 ways sex hormones might act: ***Developmental effects*** take place during a critical period and put a permanent stamp on the nervous system

Activational effects are the direct influences of circulating hormones that appear when hormonal levels rise, and wane when hormonal levels drop.

What happens in puberty?

Menses is a powerful trigger factor for migraine in females not present in males



MacGregor E A et al. Neurology 2006;67:2154-2158

AMERICAN ACADEMY OF NEUROLOGY

©2006 by Lippincott Williams & Wilkins

Link between Pubertal Development and Migraine Onset

Association (odds ratios and 95% confidence intervals) of age at menarche with migraine and non-migraine headaches among young adult women in the Growing Up Today Study

	Migraine		Non-migraine headache	
Adjusted for	OR	95% CI	OR	95% CI
Age	0.93	(0.89-0.97)	1.04	(1.00-1.08)
Age and family history of migraine	0.93	(0.89-0.97)	1.04	(1.00-1.08)
Age, family history of migraine, and weight status	0.95	(0.91-0.99)	1.02	(0.98-1.06)

Earlier age at menarche predicts increased risk of developing migraine, but not non-migraine, headaches by young adulthood

Maleki N, Kurth T, Field A. *Cephalalgia 2016*

STRAW Stages start with Menarche

-5 REPRODUCTIVE—early menstrual cycle variable

-4 **REPRODUCTIVE**– peak fertility cycle is regular

-3 a/b REPRODUCTIVE cycle regular, then subtle changes in flow and length, FSH begins to vary

-2 Menopausal Transition early, cycle varies, FSH varies

-1 Menopausal Transition late, intervals of amenorrhea of over 60 days, FSH greater than 25, vasomotor symptoms likely, can last 1-3 years

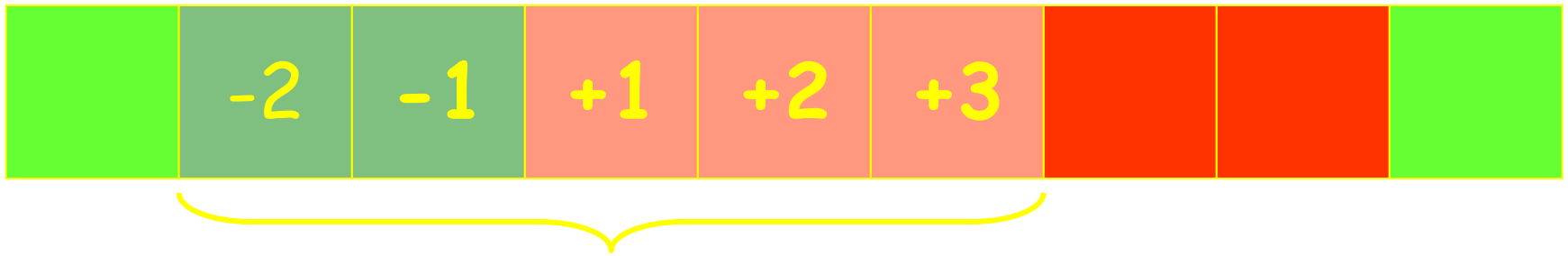
MENOPAUSE marks one year of amenorrhea

+1 a/b/c POSTMENOPAUSE FSH still elevated at first, then stabilizes, antral follicle count very low, vasomotor symptoms most likely, lasts about 2 years

+2 POSTMENOPAUSE late stage, persists for remaining lifespan

Pure menstrual migraine without aura

- Diagnostic criteria
  - Attacks, in a menstruating woman fulfilling criteria for migraine without aura
  - Attacks occur on days -2 to +3 of menstruation
    - In at least 2 out of 3 menstrual cycles
    - At NO other times of the cycle



ICHD-3 beta DEFINITION

Menstrually triggered migraine vs menstrual migraine

Definition

Can be present with random migraines as well

Migraine during pregnancy

- Background prevalence of primary headache disorders is high
  - 21-28% of women experience migraine in reproductive years
  - 80% of women with migraine will continue to experience attacks during some portion of pregnancy
- Hormonal changes of pregnancy can influence migraine expression
  - 2/3 of women experience improvement after 1st trimester
  - Migraine with aura less likely to improve
  - Migraine or migraine aura may first present in pregnancy

Sances G, Granella F et al Cephalalgia. 2003 Apr;23(3):197-205, Granella F, Sances G et al. Cephalalgia. 2000 Oct;20(8):701-7.
Granella F, Sances G et al Headache. 1993 Jul-Aug;33(7):385-9. Robbins MS et al. Neurology. 2015 Sep 22;85(12):1024-30.

Pregnancy safety of selected acute treatments

Preferred	Second line	Avoid when possible	Always avoid
Acetaminophen	Triptans	Aspirin	Ergots (dihydroergotamine, ergotamine)
Diphenhydramine	Butalbital	Indomethacin	*Lasmiditan (↑ fetal malformations at therapeutic doses in rabbit studies)*
Lidocaine SQ	Ondansetron	Opiates	
Metoclopramide	Prednisone (short acting)		
NSAIDs (*Second trimester only)	Prochlorperazine		
	Promethazine		

Burch R, Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. Headache. 2019 Oct 3; Lasmiditan product label https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211280s000lbl.pdf

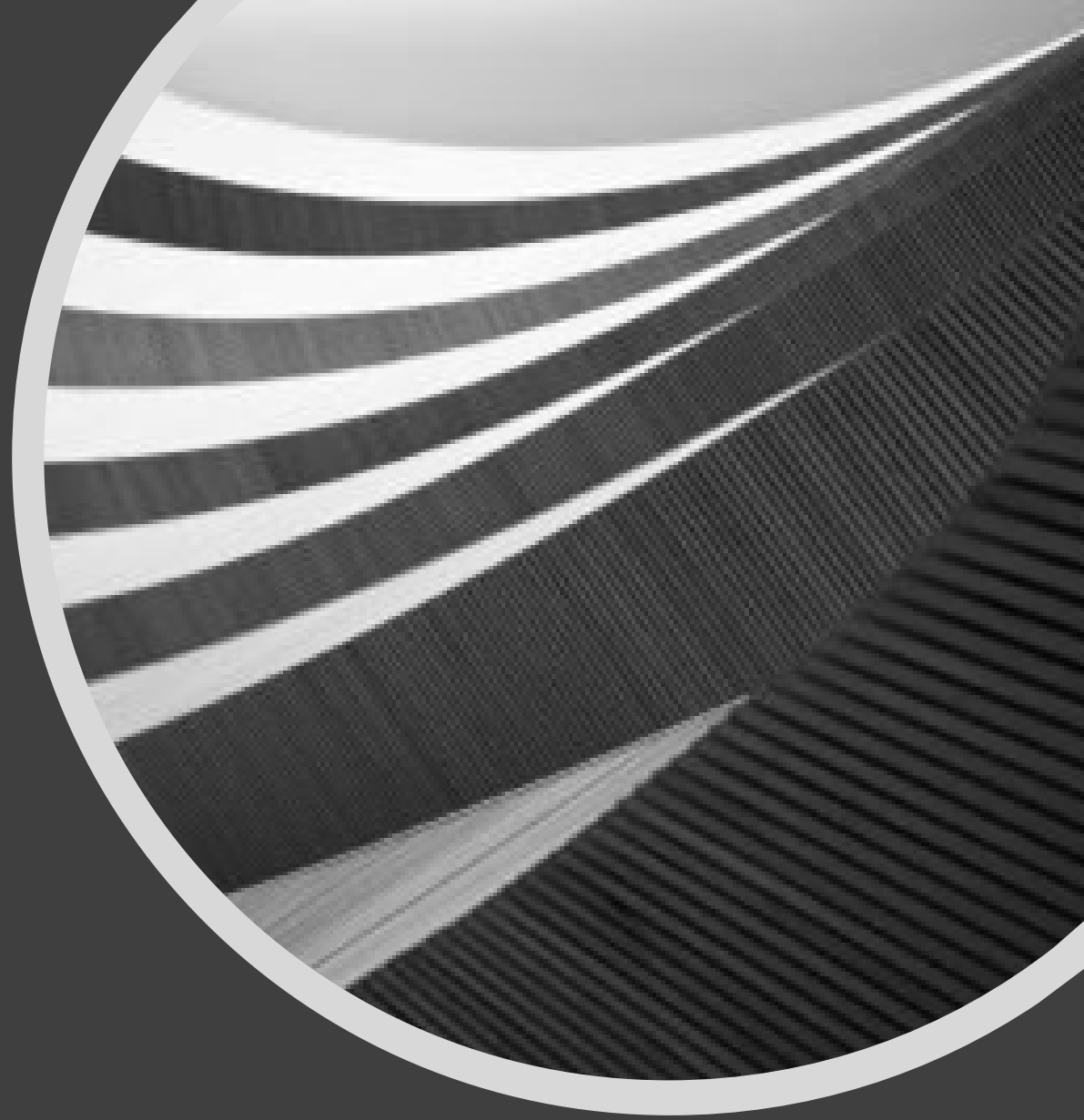
Pregnancy safety of selected preventives

Preferred	Second line	Third line	Avoid when possible	Always avoid
Propranolol	Amitriptyline	Gabapentin	Candesartan	Feverfew
	CoQ10	Magnesium	CGRP monoclonal antibodies	Valproic acid
	Cyclobenzaprine	Pregabalin	Lisinopril	Methergine
	Memantine	Vitamin B2	Onabotulinum Toxin A	CGRP antagonists
	Nortriptyline		Topiramate	
	Venlafaxine			
	Verapamil		*Safety of high dose herbs and supplements not studied	

Burch R, Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. Headache. 2019 Oct 3

Integrative Treatments

- CBT
- Acupuncture
- Nutrition
- Craniosacral therapy
- yoga



Post-partum

Return to baseline

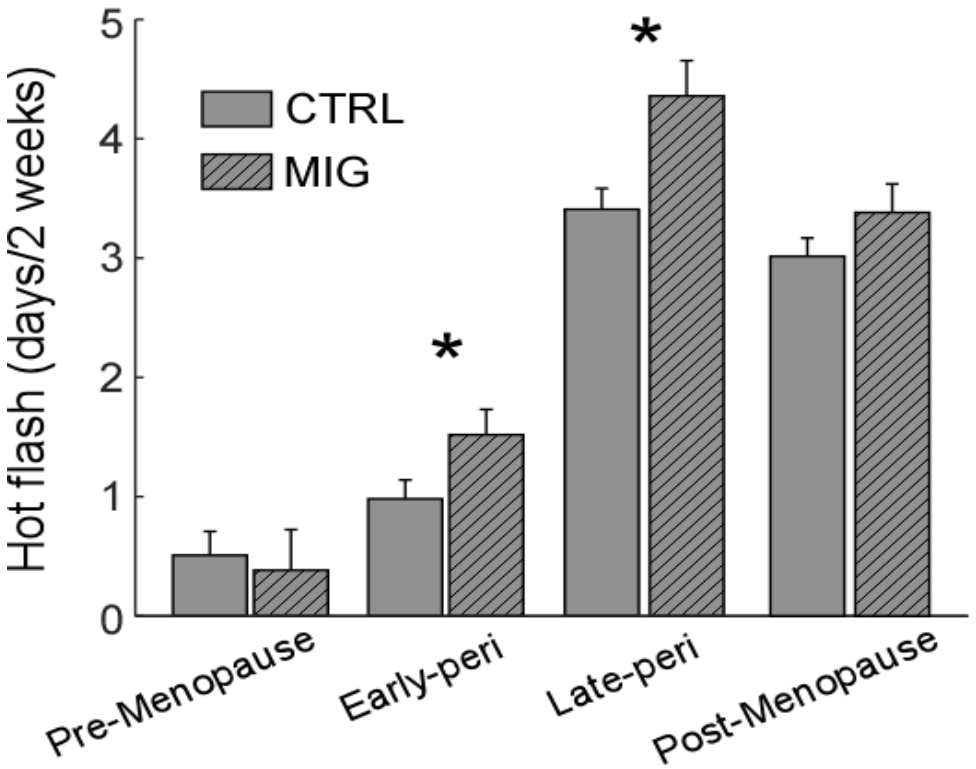
Issues with breastfeeding

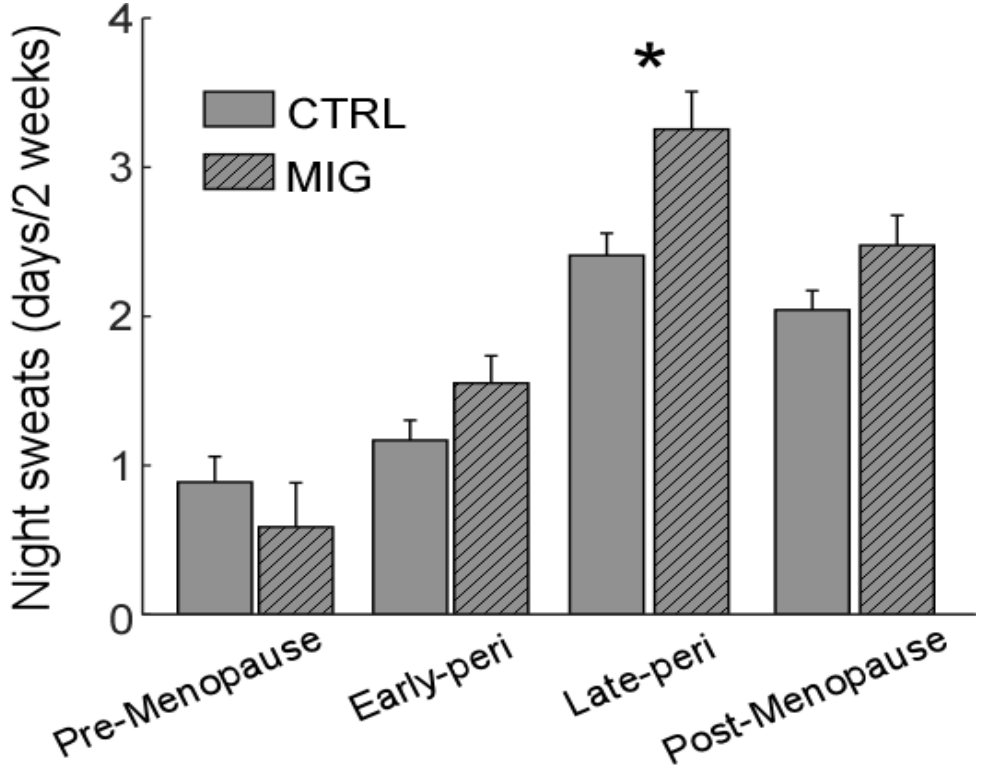
Perimenopause

- Worsening migraine
- Changes in stable pattern
- Increase in aura

- Definition
- Guidelines for treatment of climacteric symptoms

Vasomotor Symptoms and Menopause Stages





Maleki et al., Annals of Neurology, 2019

- Migraine **prevalence increases during peri-menopause** and decreases after post-menopausal stage. (Wang, Headache, 2003)
- The risk of **high frequency headache** is related to perimenopause. (Martin et al , Headache, 2016)

Stroke Risk

- Migraine with aura
- Migraine in women
- Increases with age
- comorbidities

Migraines and hormone replacement therapy

- Women's Health Study: migraine in HRT vs non-HRT OR 1.42
- Cross sectional questionnaire of 6000 women: headache and HRT OR 1.3
- Retrospective study of 120 women in a headache clinic: 64% reported improvement of migraine with HRT.
- Nonoral formulations better
- Lower doses better
- What about stroke risk?
  - OXVASC study: ~93,000 participants, 668 cryptogenic strokes
  - Trend toward ↑ risk in HRT users with migraine, but not statistically significant

MacGregor, EA. Migraine, Menopause and Hormone Replacement Therapy. Post Reprod Health. 2018 March; 24 (1): 11-18

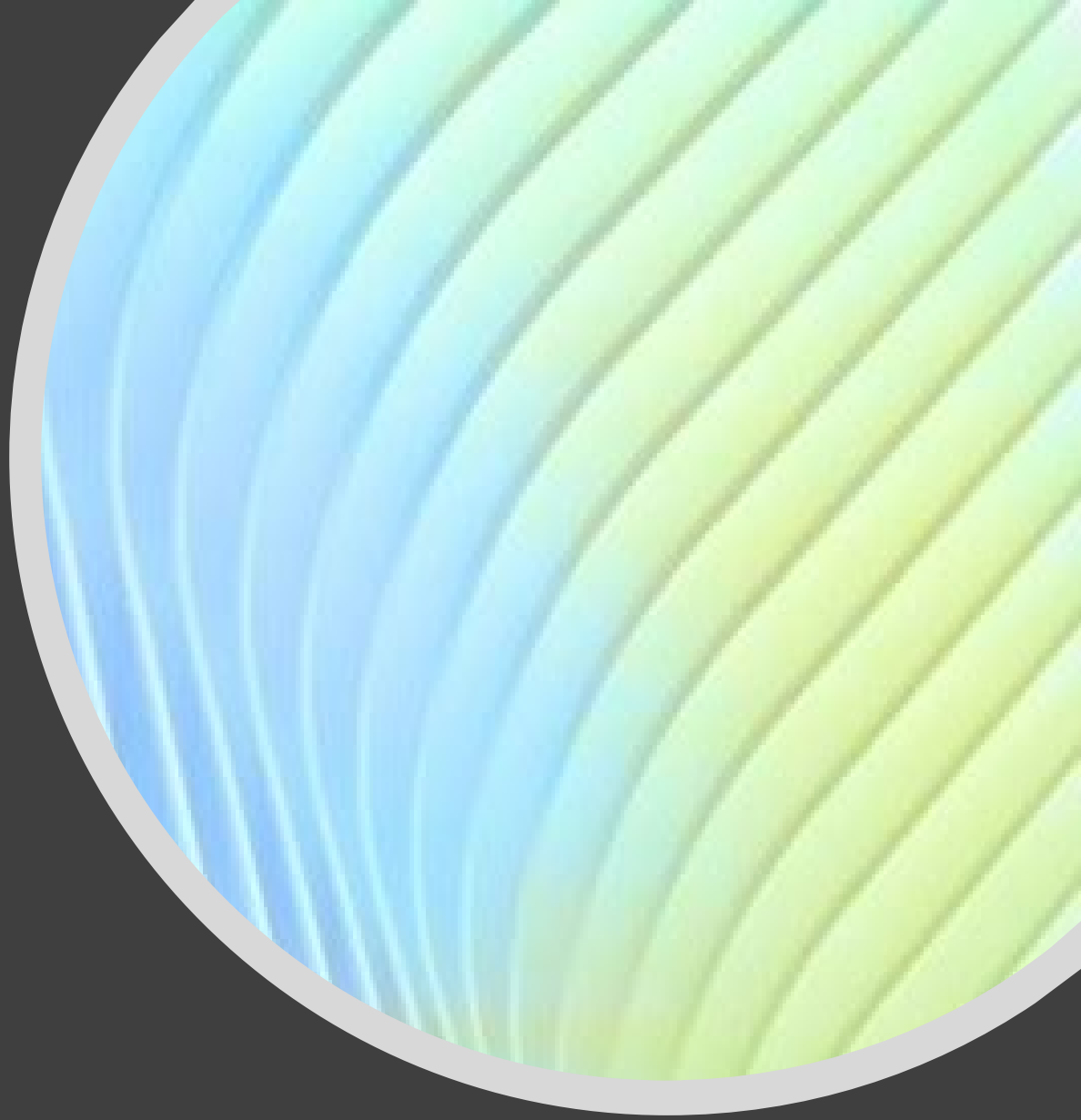
Menopause

- Migraines may not disappear
- Predictors?
- Treatment
- Length of time

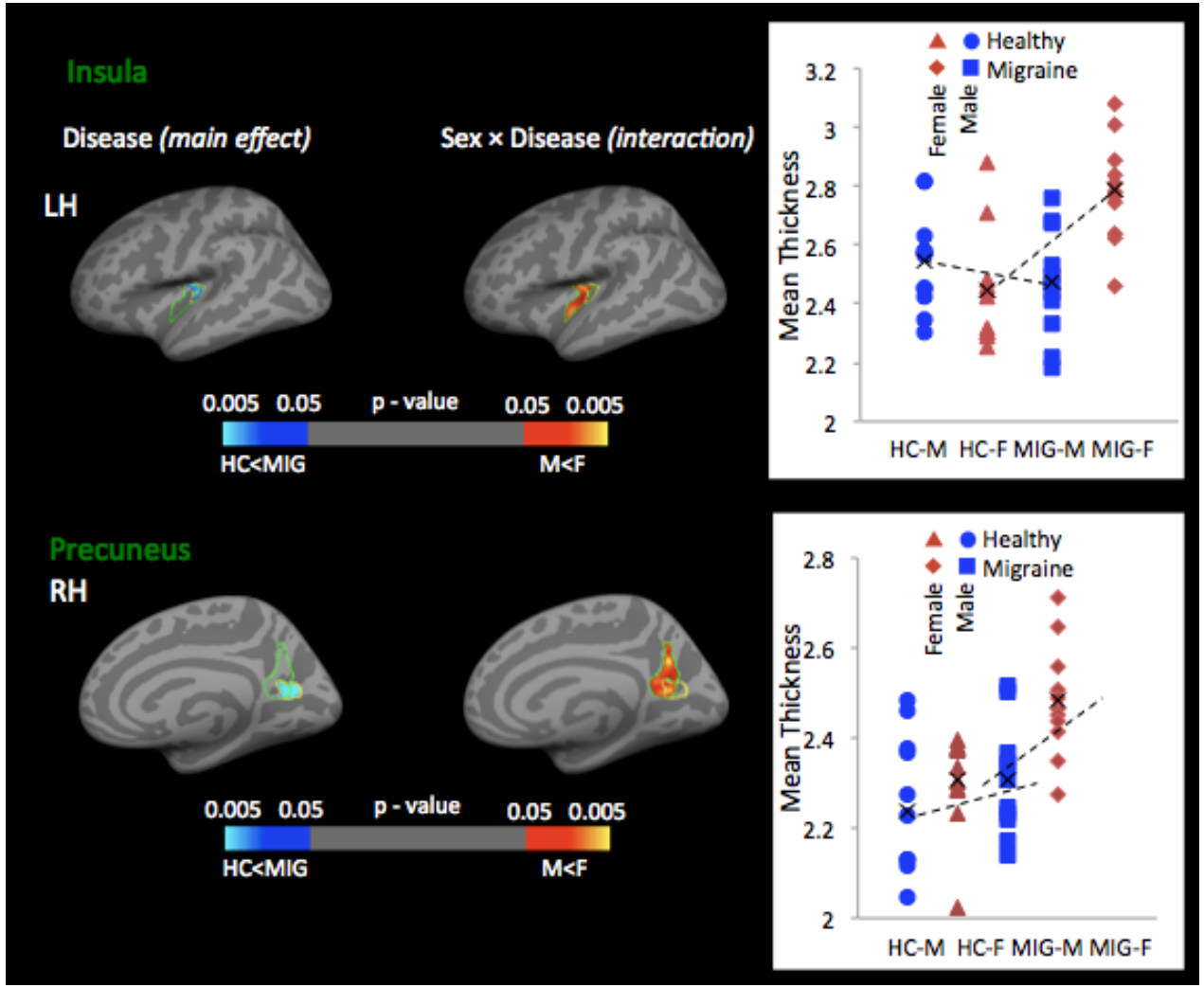
What’s missing?

Women's Brains are Different

- Imaging studies
- Pain modulating areas
- Stroke risk
- Effects of hormones

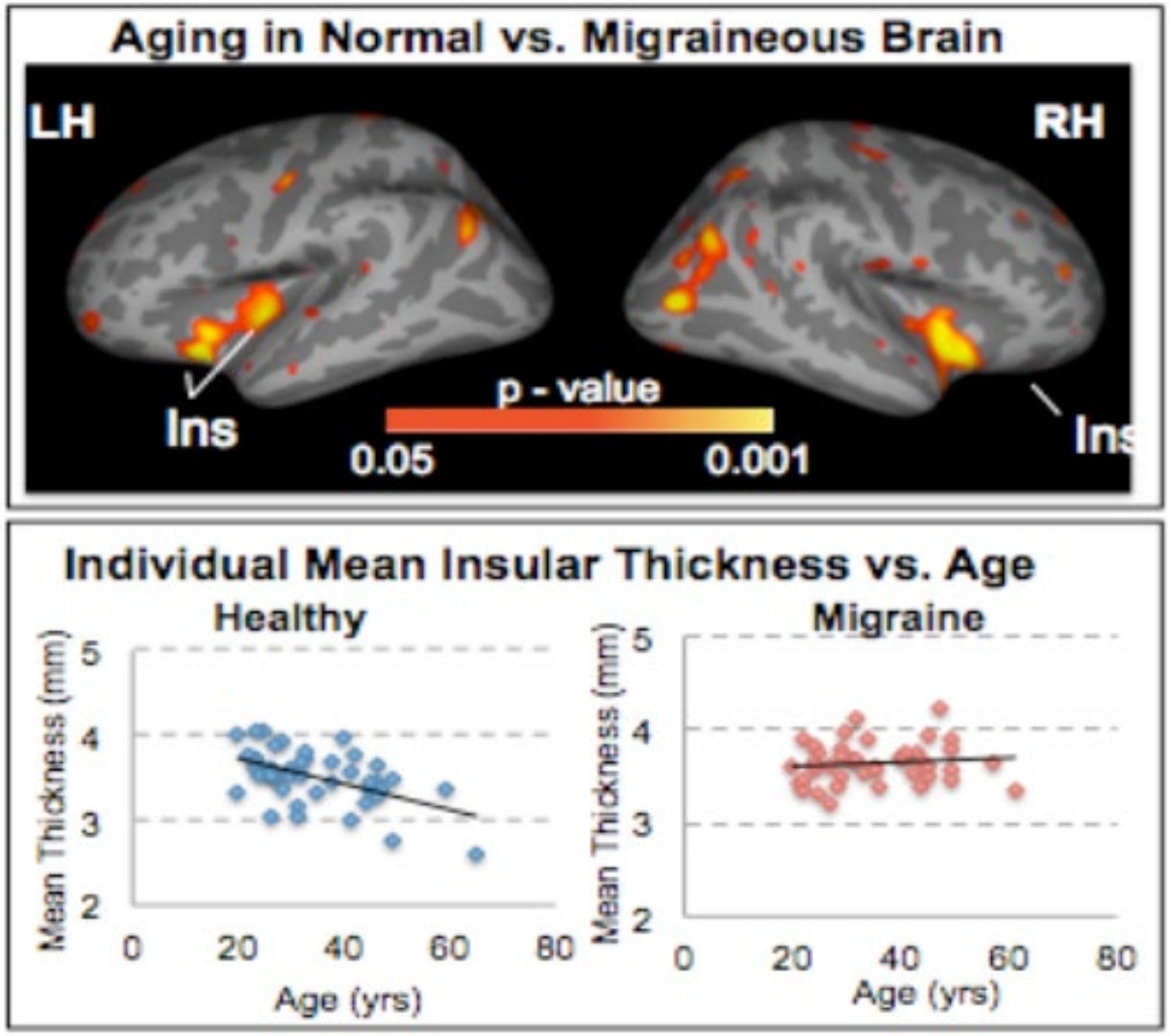


Sex-related cortical thickness differences



Maleki et al., *Brain*, 2012

Abnormal Pattern Of Insular Thinning with Age



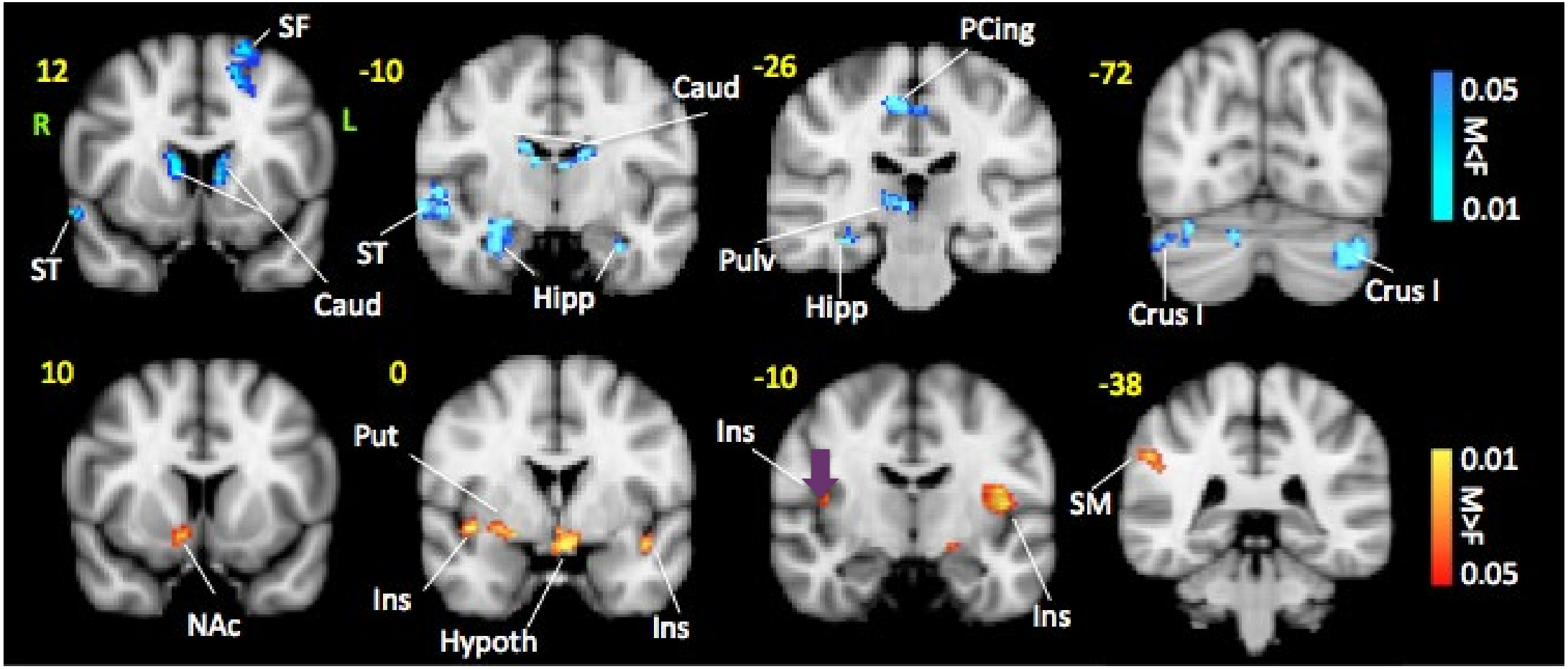
Maleki et al., *PAIN*, 2015

Imaging studies

- Female migraineurs have more disorganization of the resting state network
- Connectivity between the default mode network and executive control network is modulated by phase of the menstrual cycle, and by OCP use
- Insular and Precuneus (part of the DMN) thickness increased in female migraineurs
- White matter hyperintensities increased in female migraineurs but not males

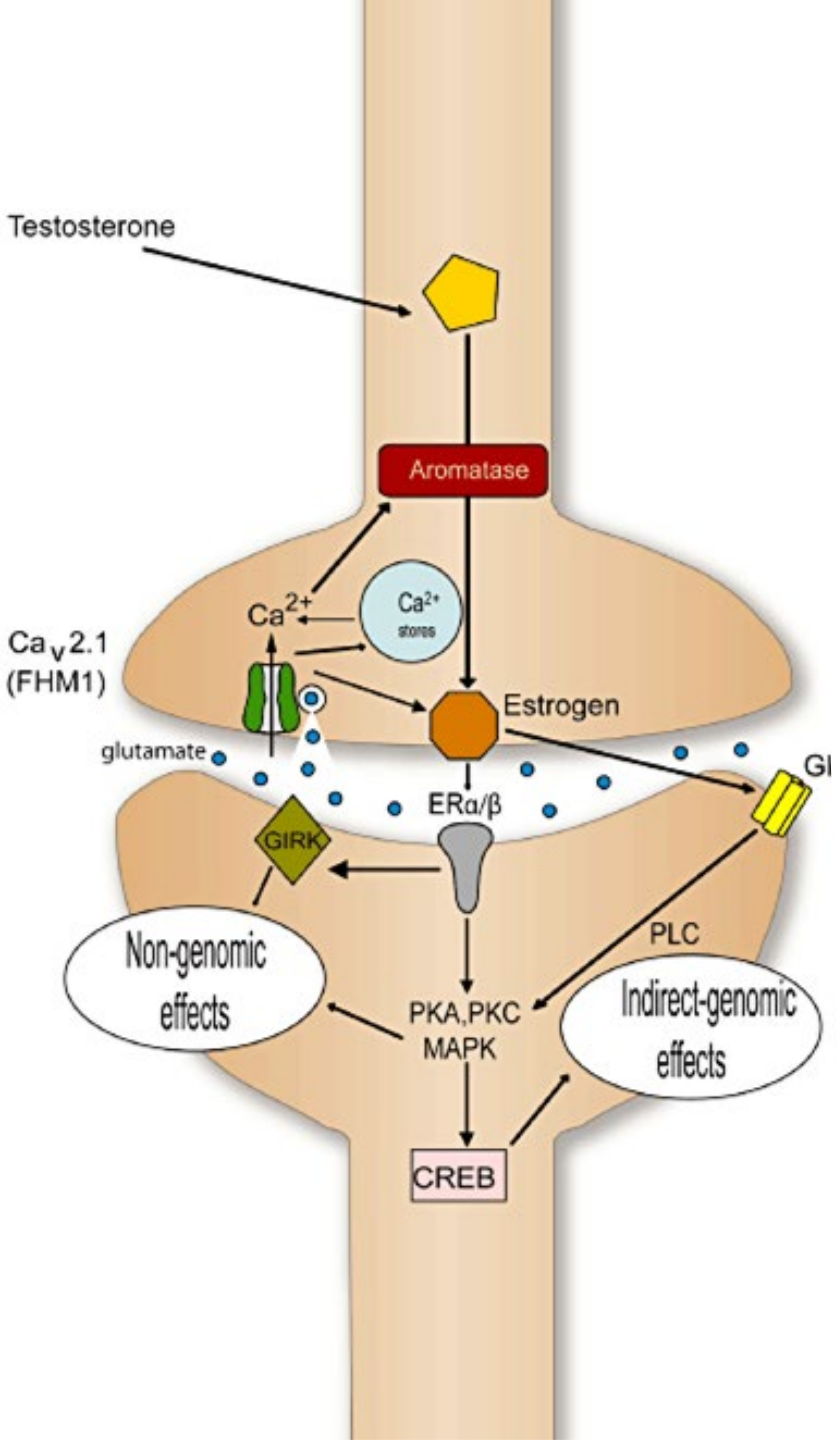
- Pavlovic JM et al J Neurosci Res. 2017 Jan 2;95(1-2):587-593

Response to Noxious Stimulation of the Hand



Female migraineurs show greater activation in brain regions involved in emotional processing

Maleki et al., *Brain*, 2012



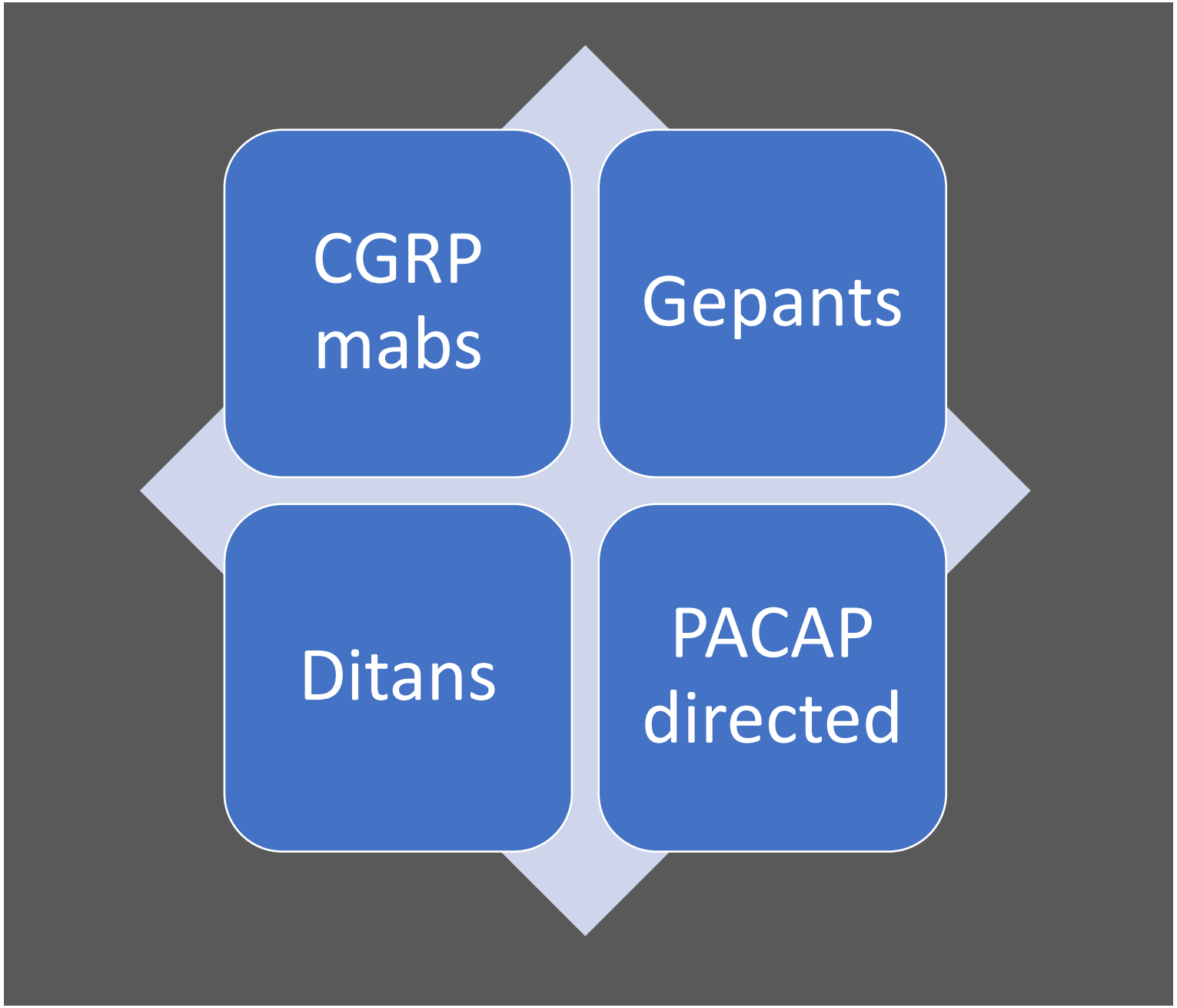
"… It is plausible that through these complex mechanisms, estrogen affects neuronal activity which affects susceptibility to CSD."

Headache. 2011 Jun;51(6):880-90. doi: 10.1111/j.1526-4610.2011.01913.x.

Migraine genes and the relation to gender.

Shyti R, de Vries B, van den Maagdenberg A.

Newer Medication Options *not for use in people who are pregnant or breast-feeding*



Case Study Migraine Clinic

PATIENT AK

AGE 45

MIGRAINE WITH VISUAL AURA SEVERAL TIMES PER MONTH

SCINTILLATING SCOTOMA FOLLOWED BY UNILATERAL SEVERE THROBBING HEADACHE WITH NAUSEA

USED SUMATRIPTAN AS ABORTIVE

Questions and Concerns?

getting remarried

Menstrual cycle is regular

What are the concerns to think about?

Contraception

Safety with migraine with aura

PCP is treating

- Preventive med?
- Contraception?

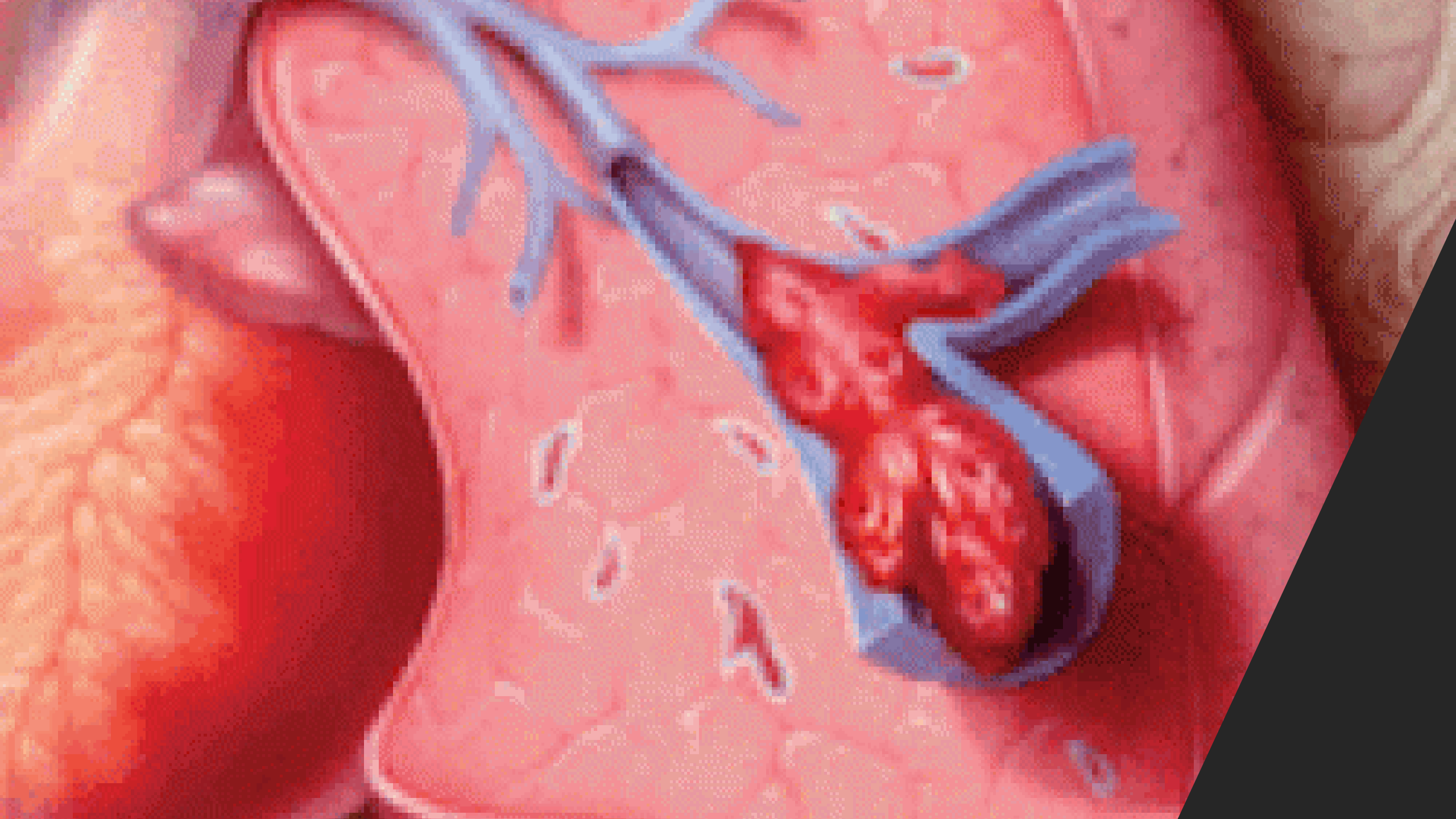
Prescribed Estrogen Progesterone topical patch in contraceptive formulation

Reflections?
Concerns?

Patient returns to clinic in two weeks with leg cramps

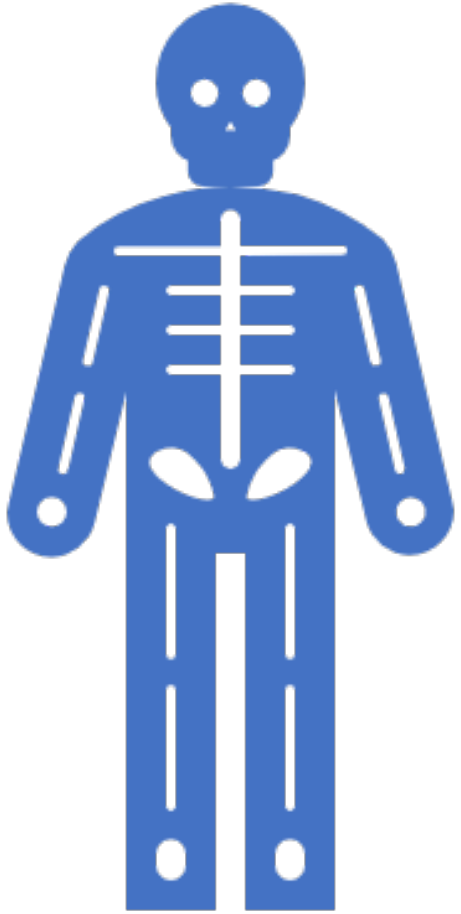
Told it was “muscular”

But then she goes to ED with SOB



What further tests would you do?

- Dopplers of LE
- Bilateral clot



Management

- Stops using the patch
- Starts on warfarin

What would treatment look like in 2025?

DOAC

But then becomes acutely short of breath again

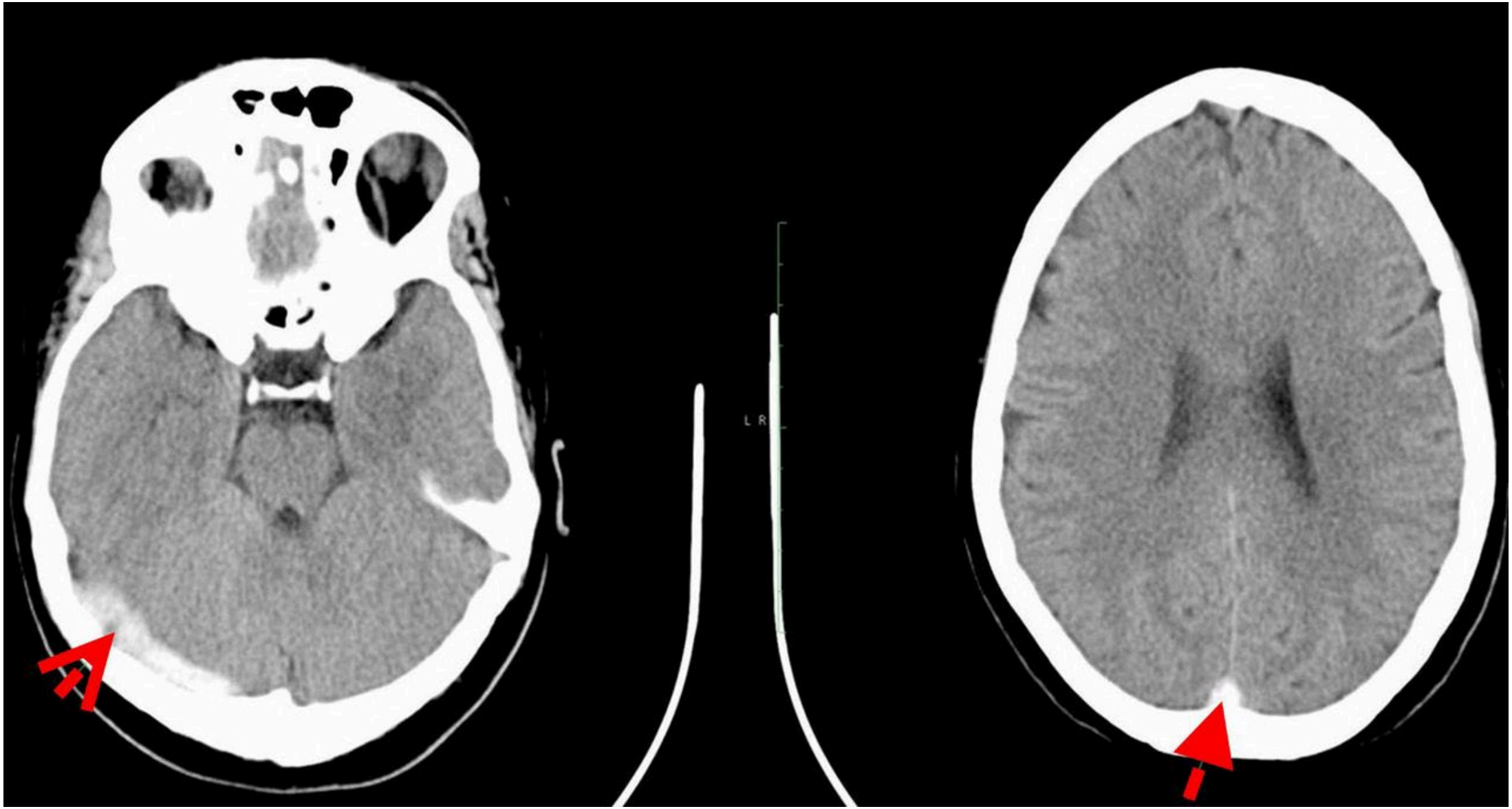
Showers of pulmonary emboli

IVF placed

And then she gets a headache

and it’s different and global
and doesn’t stop

and she develops hemibody
weakness



Now what?

- Maxed on warfarin
- Added aspirin
- Headache persisted
- Thought about LP, concerned about holding warfarin

Added acetazolamide

Reflections

FATHER WAS FACTOR V LEIDEN POSITIVE

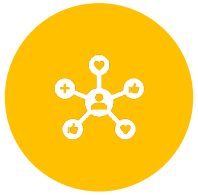
PATIENT WAS AS WELL, DISCOVERED IN RETROSPECT

MIGRAINE WITH AURA, FREQUENT EVENTS, ALL WITH AURA

How else to approach this patient case?

Need for a preventive?

Screening for aura?



Risk/benefit

Adequate and reliable abortive treatments

Discussion with every patient who could get pregnant best-practice contraception

Need for more study about female specific issues around migraine

Thank you for your attention