UPDATE IN MIGRAINE: PERIMENOPAUSE, MENOPAUSE AND MIGRAINE TREATMENT IMPLICATIONS

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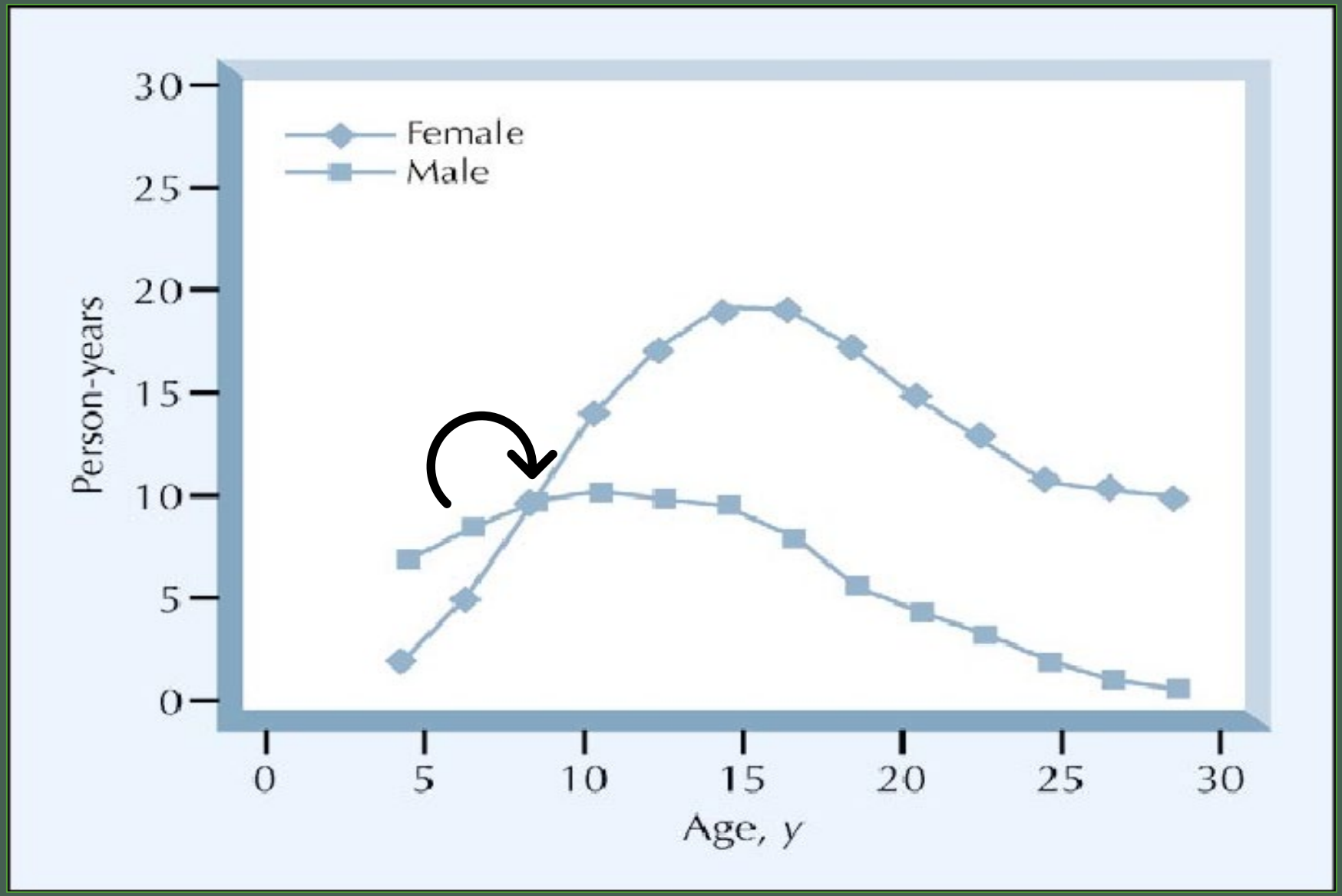
Prevalence of Migraine

- Over 30 million migraineurs in US[1]
- Migraine 3 times more common in women than men during reproductive years[1]
  - Believed to be associated with hormonal fluctuations in women; no comparable fluctuations in androgens are observed in men[2]
  - Prevalence in women rises after puberty and falls in postmenopausal period[1]
  - 51% to 55% of women with migraine report menstruation as trigger for migraine[2,3]
- Two main types of estrogen-mediated migraine[2]
  - Estrogen ***withdrawa***l and migraine without aura
  - ***High*** estrogen and migraine with aura

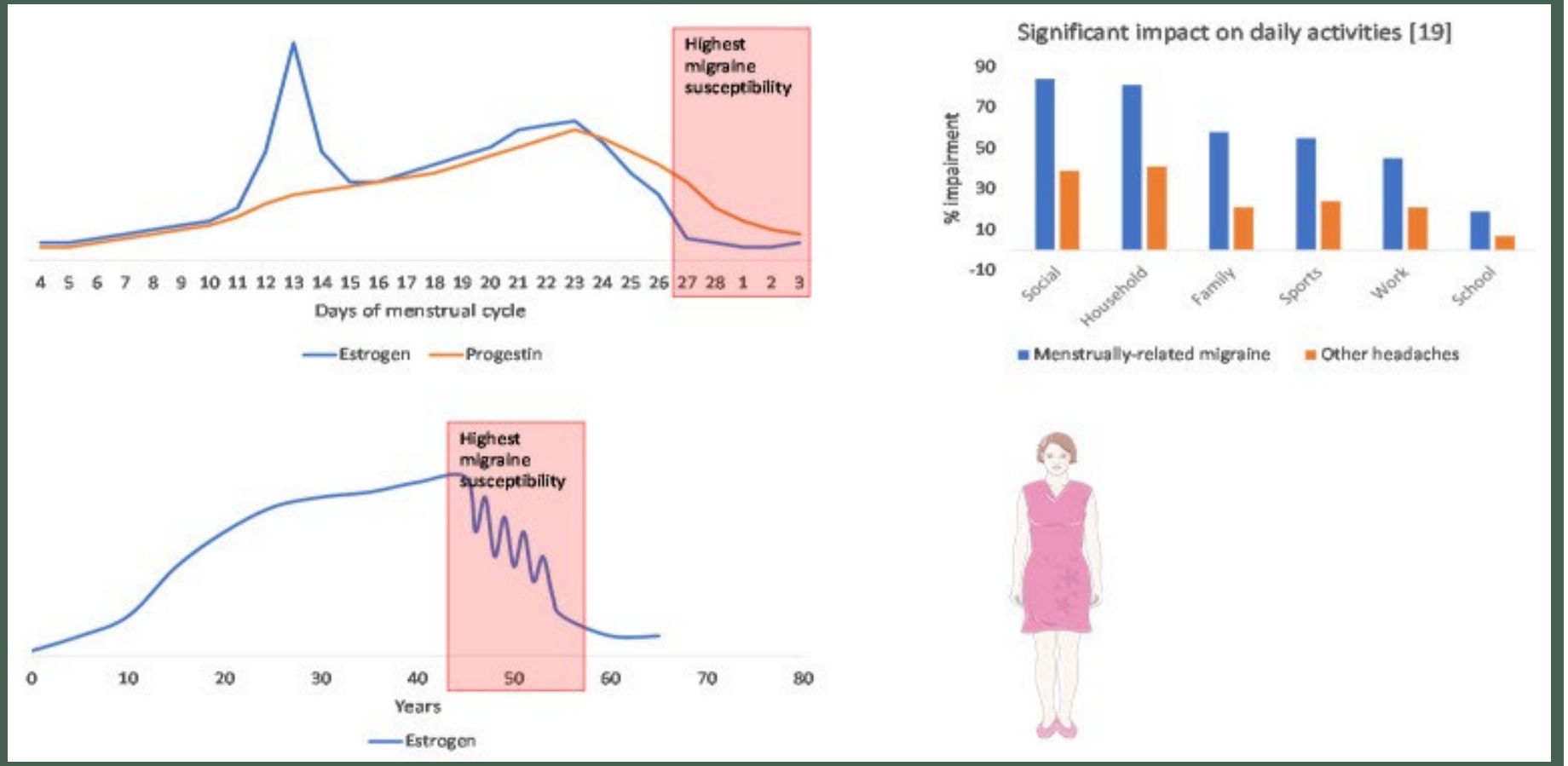
1. Lipton RB. *Headache*. 2001;41:638-645. 2. MacGregor EA. *Neurology*. 2004;63:351-353. 3. Couturier E. *Cephalalgia*. 2003;23:302-308.

Incidence of Migraine by Sex and Age



Bigal,Marcelo, Richard Lipton. Migraine at All Ages. **Current Pain and Headache Reports** 2006, **10:**207–213

Levels of sex hormones during the menstrual cycle and during the years of women's lives

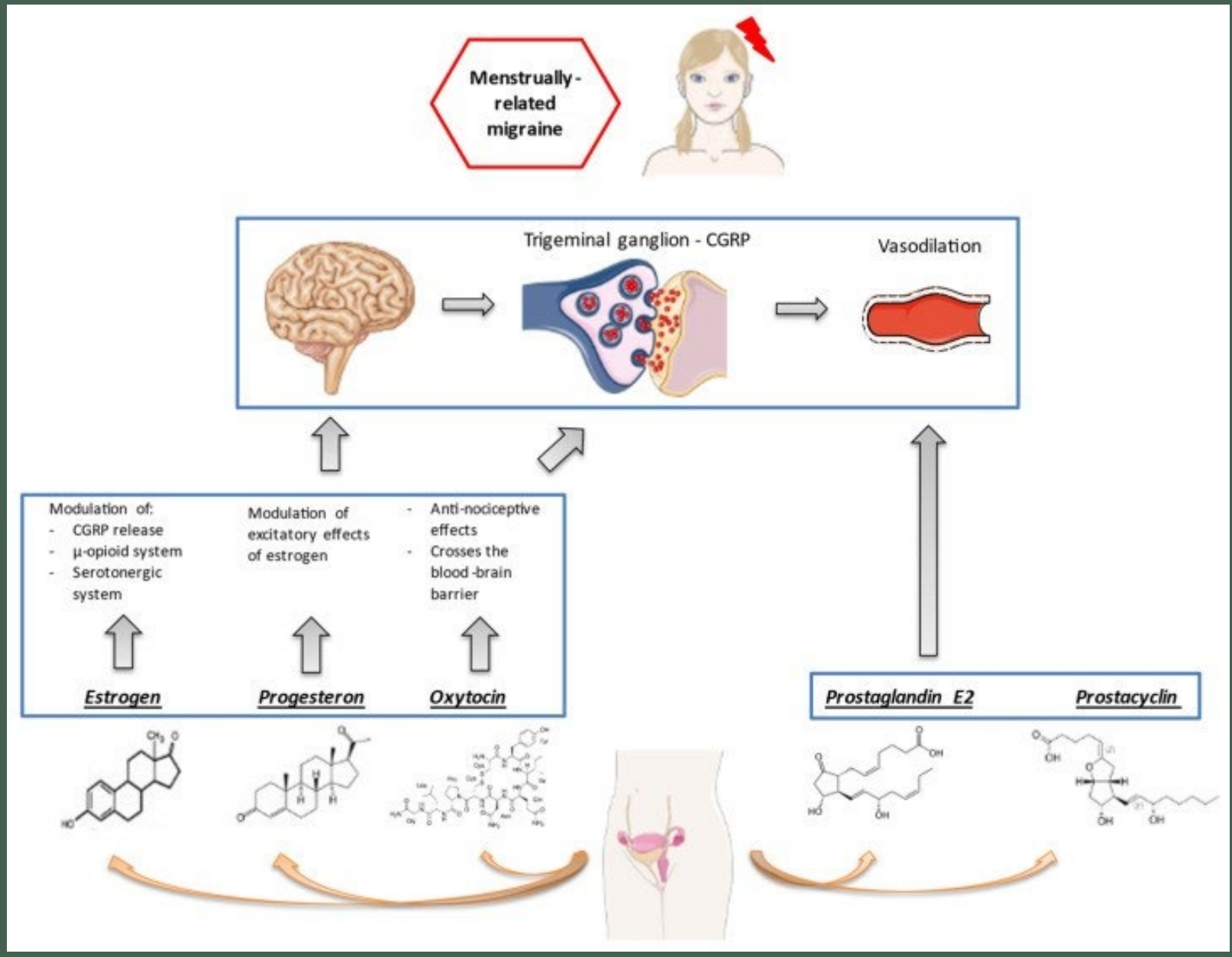


Quality of life impairment with migraine

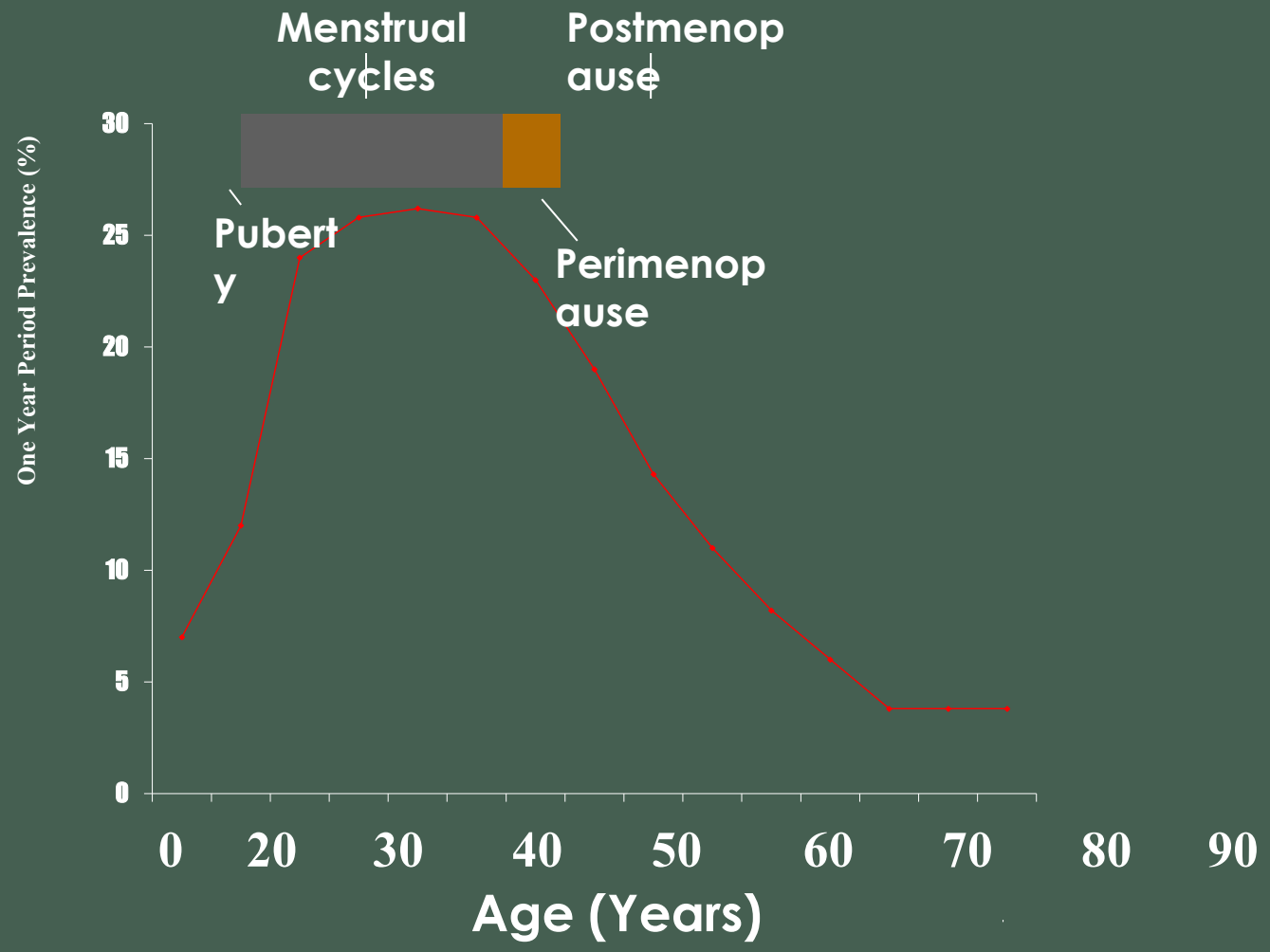
Adapted from R Ornello, 2021, J Clinical Med. and Couturier EGM, Cephalalgia, 2003.

Female Sex Hormones and Pathogenesis of Menstrual Migraine

from
Ornello, R
J Clin Med
2021,10,2263



Migraine Prevalence and Phases of the Reproductive Cycle as a Percentage of Total Life Span



Markers of Hormonal Sensitivity or Predictors

- Onset at menarche
- Menstrual migraine
- Improvement or Worsening during Pregnancy
- Previous response to OCP or HRT or Surgical Menopause

First Steps
taking the hormonal history

- Age of onset of "any" headache
- Age at onset of menstruation  headache
- Hx of oral contraceptive use  headache
- Pregnancy and Lactation  headache
- Gynecological Status: ovaries/uterus intact or not
- Hx of HRT/fertility tx/ any hormonal or surgical manipulation  headache
- Family history for headache and gyn cancers

Therapeutic Options and Management Strategies

- Acute (abortive) Therapy
  - Aborts pain and migraine-associated symptoms after headache begins
- Short-Term Prevention
  - Prevents recurring migraine attacks which are typically associated with menses
- Long-Term Continuous Prevention
  - Aimed at preventing the onset of pain
    - Ongoing prevention may be used for patients who experience migraine throughout cycle or with concomitant medical conditions
- Education/Behavior Modification

Acute Treatments

NSAIDs/Combinations[1]
- Naproxen Sodium 500-550mg, max 1375mg/day
- Diclofenac powder for oral solution 50mg, max 50mg/day. Tabs 50mg, max 150mg/day
- Acetaminophen 250mg/aspirin 250mg/caffeine 65mg, 2 capsules, max 8caps/day

Triptans[2]
- Almotriptan 6.25-12.5mg, max 25mg/day
- Eletriptan 40mg, max 80mg/day
- Zolmitriptan PO, intranasal 5mg, 10mg/day
- Naratriptan 2.5mg, max 5mg/day
- Rizatriptan 10mg, max 30mg/day
- Sumatriptan PO, intranasal, subcutaneous
- Sumatriptan 85/Naproxen 500mg 1 tab, max 2 tabs/day
- Frovatriptan 2.5mg, mg, max 7.5mg/day

Ergots[1]
- Dihydroergotamine intranasal 0.5mg, max 4mg/day subcutaneous 0.5-1mg max 3mg/day , IM injection 0.5-1mg max 3mg/day

Gepants

Atogepant 10-30-60mg
Ubrogepant 50-100mg
Rimegepant 75mg

Ditans

Lasmiditan 100mg-200mg

Anti-emetics
- Metoclopramide 5-10mg
- Ondansetron 4-8mg PO, ODT
- Prochlorperazine 10mg PO, max 40mg/day/suppositories 10-25mg, max 50mg/day

1. Becker, Werner. Acute Migraine Treatment. Continuum (Minneap Minn) ;21 (4)953-972 2. MacGregor, Anne. Migraine Management During Menstruation and Menopause. Continuum (Minneap Minn) 2015;21(4):990–1003

Non-Invasive Neuromodulation Device Options

- Transcutaneous Supraorbital Neurostimulator – sending electrical pulses through forehead to stimulates the supraorbital nerves which transmit that signal to the brain
- Single Pulse Transcranial Magnetic Stimulator – a magnet using split-second impulses to interrupt the electrical activity during migraine attacks
- Vagus Nerve Stimulator – handheld device sending mild electrical pulses to interrupt migraine
- Other devices are controlled through a phone app, transmitting weak electrical pulses to stop migraine; one activating stimulation in the vestibular nerve

1.

CGRP-Abs & Influence on "Menstrual" Migraine

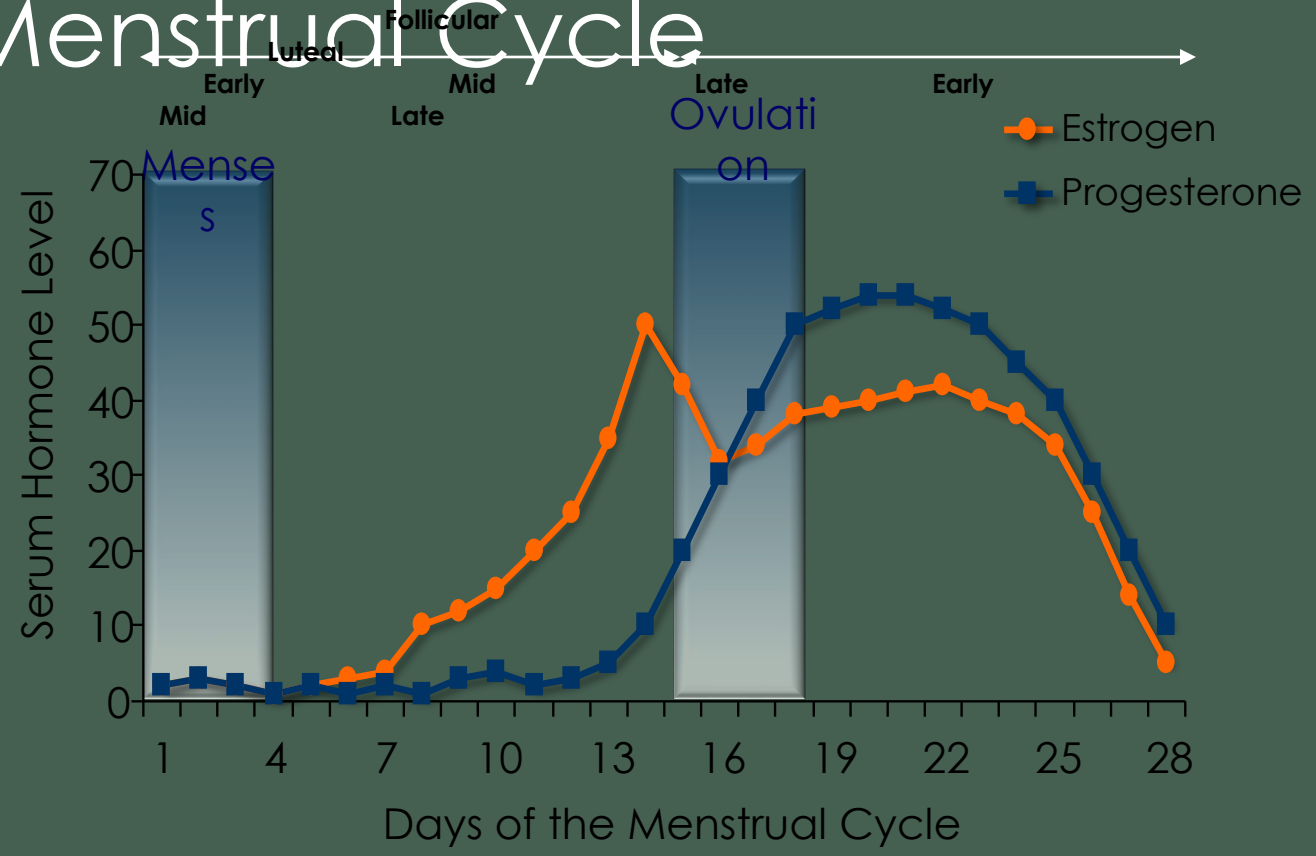
- Erenumab subgroup analysis of women with self-reported history of MRM[1]
- Endpoints
  - Reduction in monthly migraine days
  - Reduction in days which acute migraine specific medication was used
- STRIVE episodic migraine trial 3
- Erenumab was found to be equally effective in reducing monthly migraine days and improving the 50% responder rate in women with and without a history of MRM[1]
- Ornello showed that women with chronic migraine on erenumab had headaches more commonly in menstrual than in premenstrual or non-menstrual days. This pattern was similar in responders and non-responders to the treatment 4

Galcanezumab post-ad hoc analysis looked at self reported menstrual migraines (2days prior to and 3 days after onset of menses)[2]

- Migraine headache days were reduced both within the peri-menstrual period as well as outside the peri-menstrual period[2]

1.Pavlovic,Jelena, Koen Paemeleire, et al. Efficeacy of Erenumab in Women with and without a History of Menstraully-Related Migraine. Neurology Apr 2018,90(15 supplement) P4.096
2. Data on file, Eli Lilly and Company
3, Pavlovic JM et.al The Journal of Headache and Pain. 21, 03 August 2020. 4. Ornello R et.al Brain Sci 2021 mar; 11(3): 370.

Hormonal Changes During the Female Menstrual Cycle



Martin V. *Headache*. 2006; 46:3-23.

During perimenopause…..

- Estradiol levels actually increase
- Estradiol levels often higher than those of the premenopausal years
- Estrogen receptors may be increased in tissues
- In contrast, estrogen declines markedly in first year after last menstrual period, afterwards is low and stable

"Menopausal" Symptoms, ***really*** Perimenopausal

- Hot flashes
- Nightsweats
- Cycle irregularity
- Skin changes
- Decreased libido
- Dyspareunia
- Joint and muscle pain
- ***Migraine***
- ***Tension-type HA***
- Memory loss
- Mood swings
- Anxiety/Depression
- Fatigue
- Sleep Fragmentation

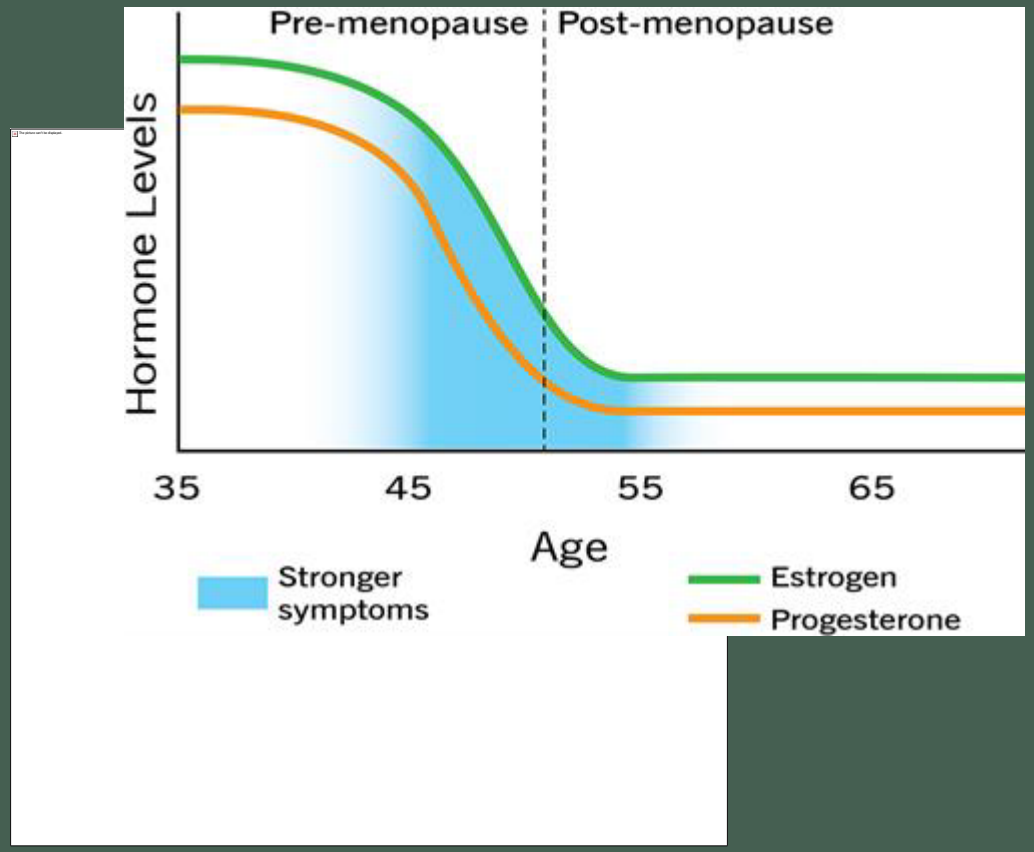
Table I.

A 'diagnosis' of early perimenopause can be made in midlife women who continue to have regular flow if they are experiencing – *any 3* of these nine experience changes.

1. New onset heavy and/or longer flow
2. Shorter menstrual cycles (≤ 25 days)
3. New sore, swollen or lumpy breasts
4. New mid-sleep wakening
5. Increased cramps
6. Onset of night sweats, in particular premenstrually
7. New or markedly increased migraine headaches
8. New / increased premenstrual mood swings
9. Weight gain without changes in exercise or eating

Prior JC. *Facts Views Vis Obgyn*. 2011;3(2):109-120.

Estrogen and Progesterone During the Transition



Cleveland Clinic Review of Menopause, 2021

Predicting Perimenopause

- Most reliable is age
- Menstrual history
- Next most reliable are symptoms
- Exclude secondary diagnoses
- Least reliable are blood tests
  - levels of FSH (can be high)
  - inhibin B (can be low)

Vulnerability to Migraine During "Peri"-Menopause

- History of menstrual headache, often unrecognized as menstrual migraine
- History of premenstrual syndrome
- History of hormonally influenced headache, 2° OCP, pregnancy, post partum, perimenopause
- History of surgical menopause

Options in Perimenopause

- Stratified acute attack therapy
- Short term menstrual migraine prevention
- Conventional prevention
- Adjunctive hormonal therapy regimens: contraceptive or hormone replacement

Does her migraine appear to have a hormonal influence?

- Establish her trend during: menses, pregnancy, breakthrough bleeding, uterine ablation
- Determine her hormonal status
- Review her overall risk factors for vascular events:
  malignancy,osteoporosis,CHD,stroke, hx of thrombosis
- Consider hormonal therapies:
  solely: if only dealing with hormonal influence on HA
  dually: if *non*-hormonally triggered attacks prominent
  and/or if **no response** to hormonal tx

High Frequency Headache

- Premenopausal: 8%
- Perimenopausal: 12.2%, OR 1.62
- Postmenopausal: 12.0%, OR 1.76
- Depression and medication overuse significantly increased the likelihood of HFH
- Late perimenopause OR 1.72 vs. early perimenopause OR 1.22, compared with premenopausal women
- Excluded BSO/Hysterectomy/Use of HRT

- Martin, V et al. Headache 2016.

Perimenopause and OCPs

- Not always reliable in controlling migraine…yet..
- 12 studies showed an exacerbating effect, though all used ***cyclic*** dosing
- Continuous regimen dosing not well studied
- Advantages include cycle regulation and contraception
- Long term health effects of extended duration or continuous contraception regimens not documented
- Progestin only pills with 2nd generation progestins, if hypercoagulable

Cochrane Review, 2006

World Health Organization	American College of Obstetrics and Gynecology	International Headache Society
Recommend complete avoidance of combination contraceptives for women with migraine with aura regardless of age. There is no restriction for migraine without aura[1]	Recommends using alternative forms of contraceptives in certain populations of women over 35 who smoke or have migraine with "focal neurological signs"[2]	Advises that low-dose estrogen containing contraception may be prescribed in women who have simple visual aura[3]

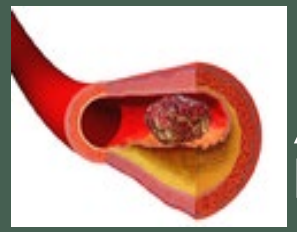
1.US Medical Eligibility Criteria for Contraceptive Use, 2010. Adapted from the WHO Medical Eligibility for Contraceptive Use, 4th Edition. CDC MMWR May 28, 2010/Vol. 59.
2.ACOG Practice Bulletin No 110: Noncontraceptive uses of hormonal contraceptives. Obstet Gynecol. 2010;115:206-218.
3International Headache Society Taskforce. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. Cephalalgia 2000;20:155-6.
Hutchinson, Susan. Use of Oral Contraception in Women with Migraine. https://americanheadachesociety.org/wp-content/uploads/2018/06/Hutchinson-Contraceptives.docx.

Tailoring Estrogen Replacement Therapy for Perimenopausal Migraine

- Oral –***not*** recommended
- **Transdermal** 50 mcg/day
  - Climara® or ClimaraPro weekly
  - Estraderm®, Vivelle q3d
  - Compounded drops/gel
  - Aim for a level of 50-70 pg/ml
- Intramuscular -- controversial
- Continuous – ***not*** intermittent dosing

Ensure that adequate estrogen dose is given to avoid endogenous fluctuations

Too high a dose, coupled with endogenous estrogen surges may result in symptoms of estrogen excess



Always consider hypercoagulopathy

Will my headaches get better after menopause?

- Role of surgery
- Role of hormonal replacement
- Patterns of headache
- Aging

Clinic Based vs. Population Studies

- Few large, prospective, population-based cohort studies
- 24.4% showed headache improved during menopause
- Yet in 35.7%, headache worsened
- Bias related to clinic vs. population based studies
- In a cross-sectional, population based study of 1333 women aged 17-65, only 17% showed improvement during menopause

Lauritsen et al Current Tx Op in Neur, April 2018, Karli N et al.J Headache Pain 2012,13(7), 557-565.

Migraine Prevalence in Menopause – a clinic study of 556 women

Occurrence

Postmenopausal women: 13.7% had headache

82% before menopause

Types:

62% migraine without aura

Remainder tension type headache

None had migraine with aura

Prognosis

Physiologic menopause 2/3 *improved*

Surgical menopause 2/3 *worsened*

Neri I et al. Maturitas, 1993 Jul

Characteristics of observational studies evaluating the relationship between migraine and menopause

Table 1 Characteristics of observational studies evaluating the relationships between migraine and menopause

Study (year)	Type of study	Setting	Inclusion period	Included subjects	Age range (years)	Diagnostic criteria for migraine	Migraine ascertainment	Issues addressed
Whitty and Hockaday[19] (1968)	Cross-sectional	Headache clinic	NR	63 (all), 40 (women in menopause)	22–81 (all)	Recurring throbbing headaches and, in addition, two of the following five features: unilateral headache, associated nausea with or without vomiting, visual or other sensory aura, cyclical vomiting in childhood, and a family history of migraine	Face-to-face interview	Migraine evolution during menopause
Kaiser and Meienberg[31] (1993)	Case series	Headache clinic	NR	10	44–58	ICHD-I	Face-to-face interview	Effects of HRT on migraine
Granella et al[24] (1993)	Cross-sectional	Headache clinic	1984–1990	1,300	18–70	Ad hoc Committee on Classification of headache (1984–1988) ICHD-I (1989–1990)	Face-to-face interview	Migraine type and menopause Menopause type and migraine
Neri et al[20] (1993)	Cross-sectional	Menopause clinic	1990	556	<65	ICHD-I	Face-to-face interview	Migraine evolution during menopause Menopause type and migraine
Cupini et al[22] (1995)	Cross-sectional	Headache clinic	1991–1993	268	18–80	ICHD-I	Face-to-face interview	Migraine evolution during menopause Migraine type and menopause
MacGregor[32] (1999)	Case series	Headache clinic; menopause clinic	NR	4	44–72	ICHD-I	Face-to-face interview	Effects of HRT on migraine
MacGregor[28] (1999)	Case series	Association members	NR	112	NR	NR	Face-to-face interview	Effects of HRT on migraine
MacGregor and Barnes[14] (1999)	Cross-sectional	Menopause clinic	NR	74	32–74	ICHD-I	Face-to-face interview	Migraine prevalence during menopause
Hodson et al[15] (2000)	Cross-sectional	Menopause clinic	1998	1,000	29–73	Previous physician diagnosis of migraine	Self-report questionnaire	Migraine prevalence during menopause Effects of HRT on migraine
Mueller[21] (2000)	Cross-sectional	Headache clinic	1997	451	18–80	ICHD-I	Self-report questionnaire	Migraine evolution during menopause Effects of HRT on migraine
Mattsson[25] (2003)	Cross-sectional	General population	1997–1998	728	40–74	ICHD-I	Face-to-face interview	Migraine type and menopause Migraine and menopausal symptoms
Misakian et al[29] (2003)	Cross-sectional	Clinical trial (WHS)	1995	17,107	>45	ICHD-I	Self-report questionnaire	Effects of HRT on migraine
Wang et al[16] (2003)	Cross-sectional	General population (KIWI)	1998	1,436	40–54	ICHD-I	Self-report questionnaire	Migraine prevalence during menopause Menopause type and migraine Migraine and menopausal symptoms
Aegidius et al[30] (2007)	Cross-sectional	General population (HUNT)	1995–1997	6,007	>40	ICHD-I	Self-report questionnaire	Effects of HRT on migraine
Freeman et al[17] (2008)	Cohort	General population (POAS)	1996–1997	404	35–47	Answers "yes", "no", or "unknown" on history of headache	Face-to-face interview	Migraine prevalence during menopause
Sabia et al[26] (2008)	Cohort	Managed care cohort (E3N)	1990–2000	28,118	NR	NR	Self-report questionnaire	Migraine and menopausal symptoms
Oh et al[18] (2012)	Cross-sectional	Headache clinic	2003–2005	224	40–54	ICHD-II	Face-to-face interview	Migraine prevalence during menopause Migraine evolution during menopause
Karli et al[23] (2012)	Cross-sectional	General population	2008	2,600	18–65	ICHD-II	Face-to-face interview	Migraine evolution during menopause

Abbreviations: HUNT, Nord-Trøndelag Health Study; KIWI, Kinmen Women's Health Investigation; POAS, Penn Ovarian Aging Study; WHS, Women's Health Study; ICHD-I, International Classification of Headache Disorders, 1st revision; ICHD-II, International Classification of Headache Disorders, 2nd revision; HRT, hormone replacement therapy; NR, not reported.

Ripa P, Ornello R, Degan D, Tiseo C, Stewart J, Pistoia F, Carolei A, Sacco S. Migraine in menopausal women: a systematic review. *Int J Womens Health*. 2015;7:773-782

Clinical Trials on Hormonal Therapy in Migraineurs

Table 2 Clinical trials on hormonal replacement therapy in migraineurs

Study (year)	Period of inclusion	Design	Interventions	Population	Number of subjects	Outcome(s)	Assessment periods	Main findings
Nappi et al[34] (2001)	1997–1999	Randomized, open-label	1) Transdermal estradiol 50 μg every 7 days for 28 days plus MAP 10 mg/d from 15th to 28th day 2) Oral conjugated estrogens 0.625 mg/d for 28 days plus MAP 10 mg/d for the last 14 days	Consecutive patients with spontaneous menopause and MO or TTH (ICHD-I criteria)	30 (MO), 20 (TTH)	Attack frequency, days with headache, headache severity, analgesic use	Run-in, 1, 3, 6 months	All outcomes increased in oral vs transdermal HRT in subjects with MO; no differences in subjects with TTH
Facchinetti et al[33] (2002)	1999–2000	Nonrandomized, open-label	1) Estradiol hemihydrate 1 mg/d plus norethisterone 0.5 mg/d for 28 days 2) Oral conjugated estrogens 0.625 mg/d for 28 days plus medroxyprogesterone acetate 10 mg/d in the last 14 days 3) Estradiol valerate 2 mg/d for 21 days plus cyproterone acetate 1 mg/d from day 12 to 21	Consecutive patients with spontaneous menopause and MO (ICHD-I criteria)	33	Attack frequency, days with headache, severity, analgesic use	Run-in, 1, 3, 6 months	Progressive increase in attack frequency, days with headache, and analgesic consumption in all groups after 6 months; decreased duration and increased severity of attacks; increase in number of days with headache and number of analgesics used smaller with continuous combined regimen
Nappi et al[35] (2006)	NR	Randomized, open-label	1) 1 mg 17β-estradiol +0.5 mg norethisteroneacetate 2) 2.5 mg tibolone	Consecutive patients with spontaneous menopause and MO or TTH (ICHD-I criteria)	40	Days with headache, severity, analgesic use	Run-in, 3, 6 months	Tibolone noneffective in decreasing number of days with MO; significant decrease in number of hours during which pain intensity prohibited daily activities and number of analgesics after 3 months with tibolone; continuous estroprogestin increasing the number of days with head pain and the number of analgesics; both treatments effective in the management of TTH
Martin et al[27] (2003)	NR	Randomized, placebo-controlled, pilot trial with parallel-group design	1) Subcutaneous goserelin implant +100 μg estradiol patch 2) Subcutaneous goserelin implant + placebo patch	General population and headache clinic	23 (10 estradiol patch, 13 placebo patch)	Headache index[a] (primary) Headache disability, headache severity, headache frequency, percentage of headaches with a pain severity rating of 7 or greater (secondary)	Lead-in month, three subsequent phases of 2.5 months, 1 month, and 2 months' duration, respectively	Decrease in headache index with goserelin/estradiol compared with goserelin/placebo; similar improvements in the goserelin/estradiol and goserelin/placebo group for all secondary outcome measures with the exception of headache frequency

Notes: [a]Defined as the mean of pain severity ratings (0–10 scale) recorded three times per day by the use of a daily diary.
Abbreviations: HRT, hormone replacement therapy; ICHD, International Classification of Headache Disorders, 1st revision; MAP, medroxyprogesterone acetate; MO, migraine without aura; NR, not reported; TTH, tension-type headache.

Ripa P, Ornello R, Degan D, Tiseo C, Stewart J, Pistoia F, Carolei A, Sacco S. Migraine in menopausal women: a systematic review. *Int J Womens Health*. 2015;7:773-782

Changing the strategy….

- Migraine with aura ***doubled the risk of heart attack***
- ***6,102 migraineurs and 5,243 non migraineurs***
- Migraineurs: 50% more likely than control to have diabetes, hypertension and elevated cholesterol
- May be underlying endothelial pathology

Kurth, Bigal et al 2010.

Aura vs. Frequency of Aura

- Longitudinal Women's Health Study [1]
  - 27,798 women >45years old
  - MwA conferred an increased risk of CvD (including stroke) that varied with frequency of aura
    - Aura <one a month conferred a two-fold increased risk compared to women w/o migraine.
    - Risk increased more than four-fold with aura frequency exceeded once a week.

1. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: A prospective study. Neurology. 2005;64:1020-1026.

Reasons… not well understood

- Does migraine with aura cause this increased risk?
- Or…..
- Is there ***a common factor*** causing both migraine and myocardial infarction and stroke

Cerebrovascular and Cardiovascular Risks

- Hypertension
- Migraine with aura
- Diabetes
- Smoking
- Obesity
- Family hx of early heart disease
- Hypercholesterolemia
- Hypercoagulable state

Testable Hypotheses

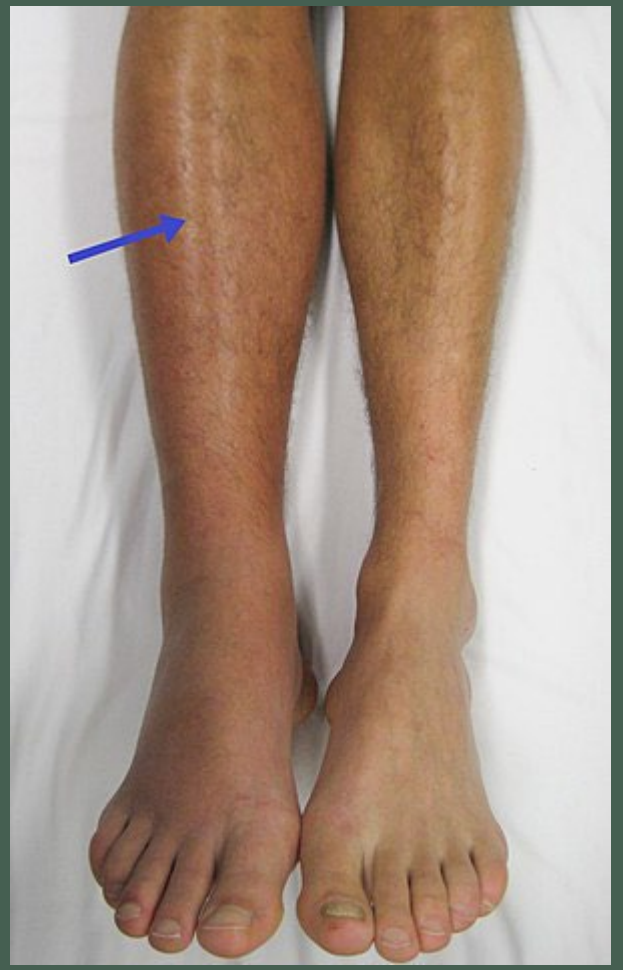
- Repeated migraine attacks associated with neurogenic inflammation cause progressive arteriopathy and increased risk of ischemic stroke.
- Vascular inflammation may be associated with stroke risk; C - Reactive Protein (CRP) is a marker of oxidative stress, inflammation, and stroke risk.
- Markers of vascular inflammation may predict stroke risk in migraine

Offer Hormonal Replacement Therapy when….

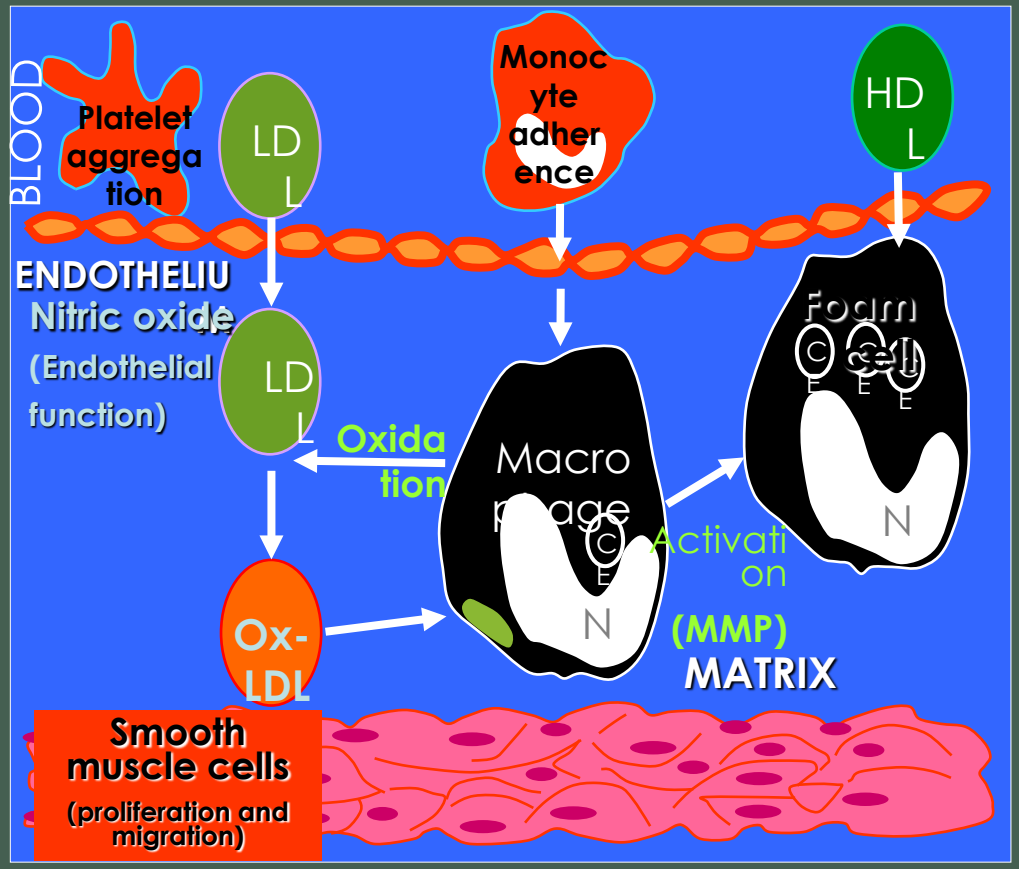
- Hormonal fluctuations appear to be a major triggering event for migraine
- High risk for colon cancer
- Significant perimenopausal symptoms: hot flashes, mood disorders, insomnia, cognitive changes
- High risk for fracture
- Be Wary: Hx of premenstrual syndrome predicted ***increased*** headache in women starting continuous combined HRT
- Evaluate for hypercoagulable risks!

Thrombotic Complications

- Risk highest in migraine with aura
- Risk highest with newer agents, drospirenone/ethinyl estradiol (Yaz), etonogestrel vaginal ring (NuvaRing) or norelgestromin-containing transdermal patch (OrthoEvra)
- Study did not include info on timing of thrombotic events or reasons for using combined hormonal contraceptives
- Cannot disentangle cause and effect
- Computerized data base – Research Patient Data Registry of Partners Healthcare



Inflammatory Effects on the Arterial Wall Leading to Atheroma



Menopause and HRT

- HRT has a variable influence on migraine:
  - Improvement (45%)
  - Worsening (46%)
  - No change (9%)

MacGregor EA. Is HRT giving you a headache? *Br Migraine Assoc Newsletter* 1993:19-24.

HRT Effect on Pain Responses in Postmenopausal Women

Groups

- Women on HRT
- Women not on HRT (Non-HRT)
- Men

Findings

- No differences in recent pain complaints or self reported health
- Thermal pain perception
  - HRT women lower pain thresholds and tolerance
  - Non-HRT/Men did not differ in thermal pain perception

Fillingim and Edwards. Pain 92 (2001);229-234

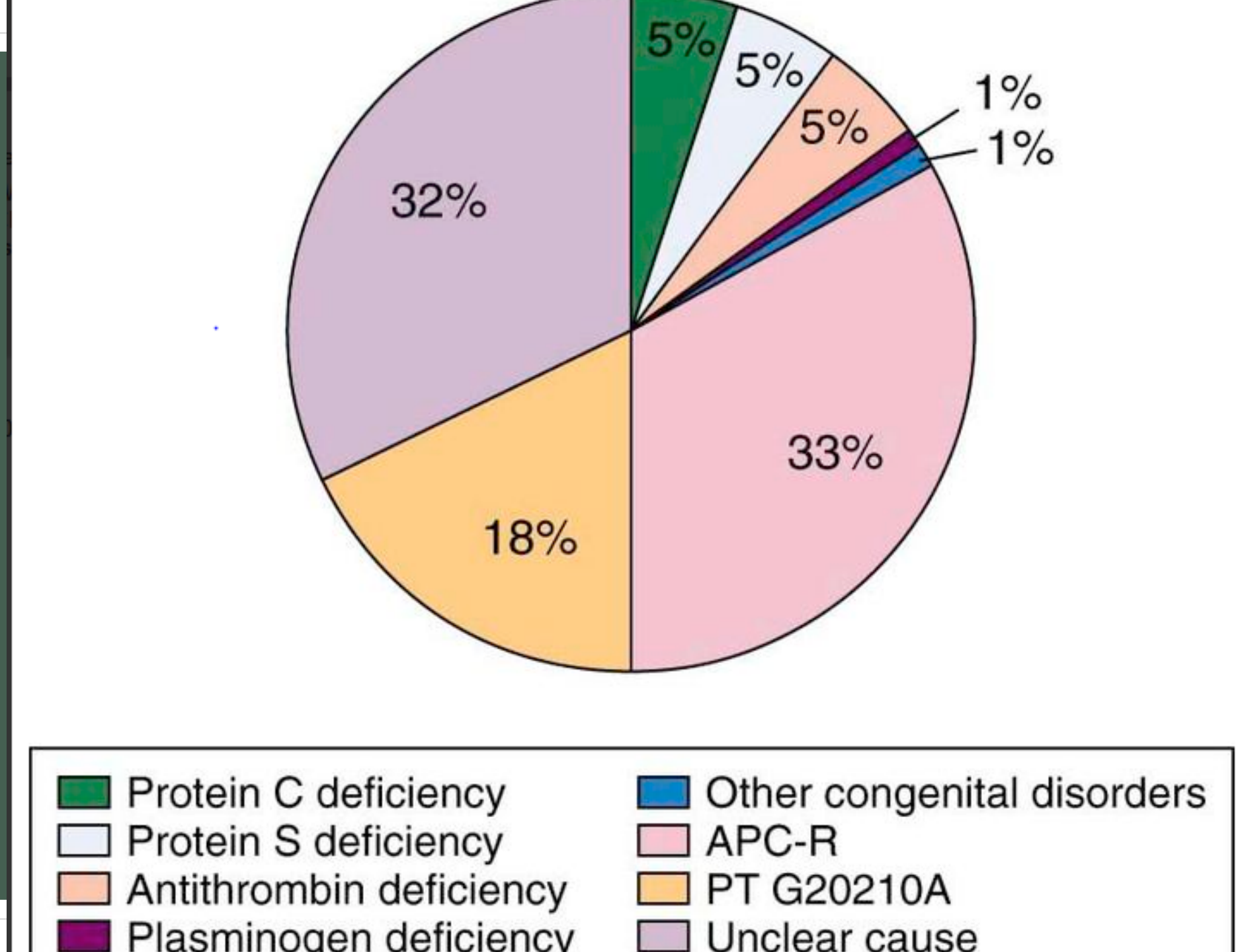
Hypercoagulable States

- **INHERITED**
- Factor V Leiden
- Prothrombin gene mutation
- Anti-thrombin deficiency
- Protein C & S deficiencies
- Elevated homocysteine
- Dysfibrinogenemia
- Elevated Factor VIII levels
- Abnormal fibrinolytic system
- Sickle Cell disease

- **ACQUIRED**
- Anti phospholipid antibody syndrome
- Supplemental estrogen use
- HIT
- Cancer
- Medications
- Central venous catheter
- Obesity
- Pregnancy

Inherited Hypercoagulable States

- Anti-thrombin III deficiency
- Protein S deficiency
- Protein C deficiency
- Activated Protein C Resistance – Factor V Leiden
- Prothrombin gene mutation
- Dysfibrinogenemias


5%
5%
5%
1%
1%
32%
33%
18%
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Plasminogen deficiency
Other congenital disorders
APC-R
PT G20210A
Unclear cause

SO WHICH TESTS TO ORDER?

Hypercoagulable workup

- PT and PTT
- Protein C
- Protein S
- Antithrombin III activity
- Prothrombin gene mutations
- Factor V Leiden gene mutation
- Activated Protein C resistance
- Anticardiolipin antibodies (IgG and IgM)
- Beta2-glycoprotein I antibodies (IgG and IgM)
- Lupus anticoagulant tests
  - dilute Russell viper venom time
  - dilute activated PTT
  - hexagonal phospholipid
- Homocysteine
- Factor VIII activity
- D-dimer
- Lipoprotein (a)
- MTHFR

HRT in 10,000 Women: Benefits

BENEFIT	Age 55-64 Meta	Age 65-74 Meta	Age 55-64 WHI	Age 65-74 WHI
Hip #	3	9	4	13
Wrist #	34	37.5	ns	ns
Vertebral #	32	57	27	49
Colon Ca	2	4	3	7
?Dementia	17	34	ns	ns

Nelson et al JAMA, 2007; 288 (7)

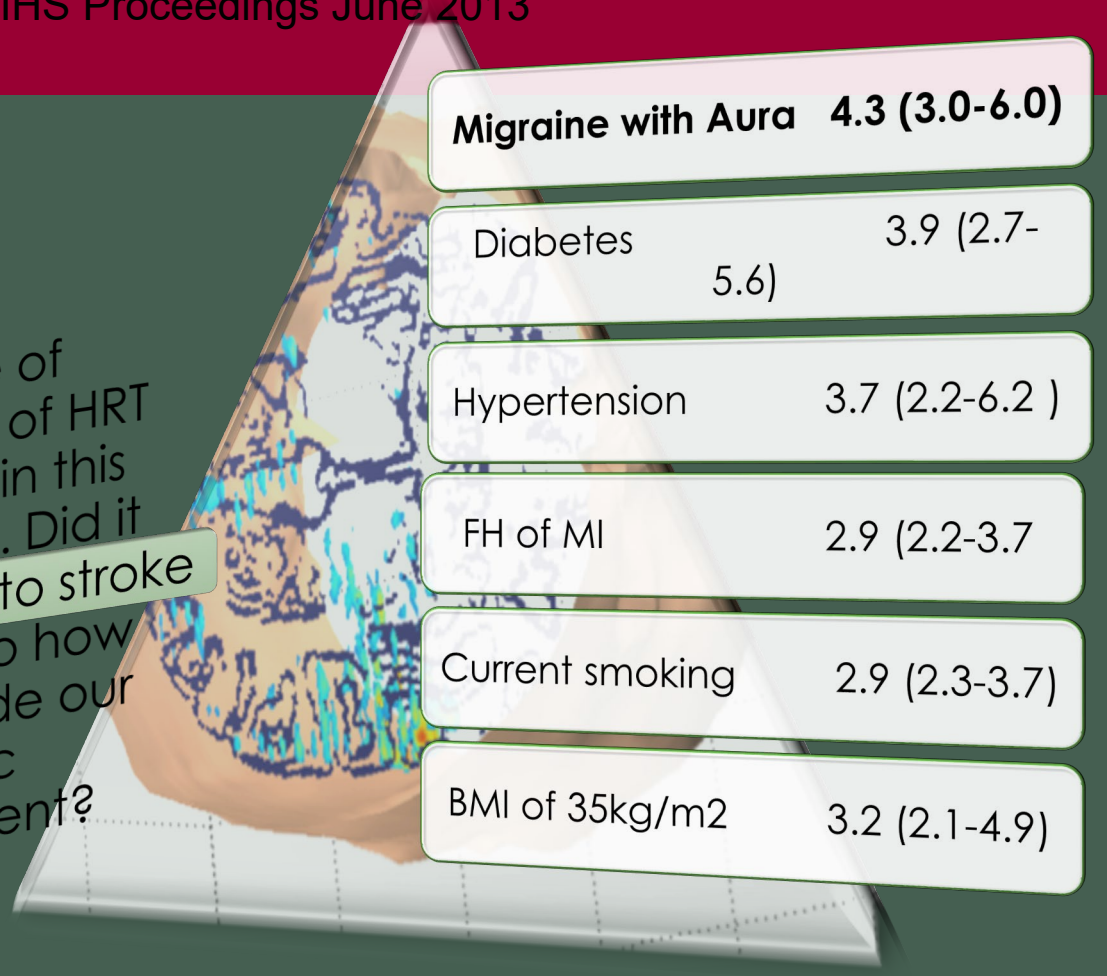
HRT in 10,000 Women: Harms

HARM	Age 55-64 Meta	Age 65-74 Meta	Age 55-64 WHI	Age 65-74 WHI
CHD	0	0	6	9
Strokes	1	3	4	9
ThrE yr1/FU	3/1.5	3/1.5	-/1.4	-/1.4
Breast Ca<5yr	0-2.5	0-6	nc	nc
Breast Ca >5yrs	7-11	10-15	8	11

Nelson et al JAMA, 2007;

Stroke Risk (Rate/yr/1000; 95% CI) in Women's Health Study

Kurth et al, IHS Proceedings June 2013



Migraine with Aura	**4.3 (3.0-6.0)**
Diabetes	3.9 (2.7-5.6)
Hypertension	3.7 (2.2-6.2)
FH of MI	2.9 (2.2-3.7
Current smoking	2.9 (2.3-3.7)
BMI of 35kg/m2	3.2 (2.1-4.9)

Raises issue of interaction of HRT and stroke in this population. Did it contribute to stroke risk and if so how does it guide our therapeutic management?

The "Dilemma" of Hormonal Therapy

- Perhaps the pendulum has begun to swing
- Timing of estrogen therapy may be key
- Women who used any type of estrogen therapy w/in 5 yrs after menopause had a 30% reduced risk of developing Alzheimer's
- But women who began estrogen therapy 5 years of more after menopause had no reduced risk

Zandi, et al 2012 Neurology, Cache County investigator group

Increased risk of dementia

- Opposed estrogen-progesterone compounds taken later in life
- Bilateral oophorectomy
- Unilateral oophorectomy
- Removing uterus alone (conserving both ovaries)

Rocca 2014 Neurology

the "critical" window

- for estrogen benefit

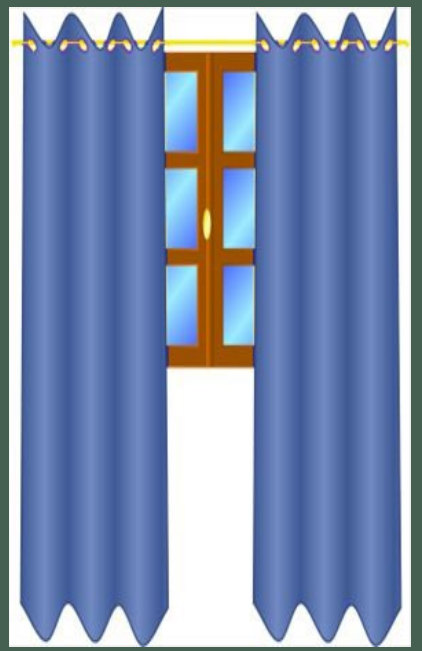
in brain.....estrogen

initiation at ***perimenopause***

necessary to observe

benefits of --neuroprotection

-- cognition



Sherwin 2007, Maki 2007, Suzuki 2007, Zhang 2009w

Reassurance from Women's Health Initiative

- No link was found between migraine hx and risk for stroke, MI, and other CVD was found in postmenopausal women
- 71,441 woman between 50-79 years of age, of whom 10.7% had migraine
- Pavlovic et al 2019, found that after 22 yr of longitudinal followup:
- 211 incident strokes in migraine/1943 stroke in women w/out migraine
- Trend continued across composite CVD events – angioplasty, CABG, CAD, DVT, PE

Revenge of Life Expectancy

- Men have a higher prevalence of

  mild cognitive impairment than women,

  but …

  women tend to be more likely to develop dementia and decline faster than men once they have the diagnosis of Alzheimer's disease

Mayo Clinic Study of Aging 2014

Estrogen Replacement Therapy

- No longer offer oral estrogen
- Transdermal 50 mcg/day
  - Climara® or ClimaraPro weekly
  - Estraderm®, Vivelle q3d
  - Compounded drops/gel
- Intramuscular -- controversial
- Continuous – ***not intermittent*** dosing

Optimizing Estrogen Dose

- Ensure that adequate estrogen dose is given to avoid endogenous fluctuations
- Tailoring treatment may pose a challenge in perimenopausal women
- Too high a dose, coupled with endogenous estrogen surges may result in symptoms of estrogen excess
- Always consider hypercoagulopathy

American College of Obstetrics and Gynecology (ACOG) and North American Menopause Society

- No scientific evidence to support claims of increased efficacy or safety for compounded estrogen or progesterone
- Saliva tests are not approved for use in guiding hormone therapy
- NAMS warns women about potential harm from custom compounded products

Mary Menopause

Mary Menopause age 49

- Horrid “menopausal” symptoms: nightsweats, sleep fragmentation, depression, frequent severe migraine
- Placed on estrogen/progesterone patch with improvement in all symptoms, including headache for three years
- Patch stopped abruptly by obgyn for concern about risk
- Worse migraine since (4 months), three failed trials of migraine prophylaxis, never offered HRT again
- Association between HRT and migraine never established by patient or physician

Mary's Needs

- Mother with severe osteoporosis
- Father with treated colon cancer
- No cardiovascular risk factors
  nonsmoker,
  normotensive, nl lipids
- Significant perimenopausal symptoms
- No need for birth control
- Negative hypercoagulable profile

Mary's treatment choices

- Offered estrogen /progesterone patch for continuous dosing
- Given triptan/NSAID for abortive therapy; plan for adjunctive prophylaxis if needed
- Begun on regular exercise program with weight-bearing
- Sleep hygiene
- Now followed in a menopause clinic! <1HA/mo!

Had Mary worsened on HRT ?

Exacerbation of Migraine on HRTx

Treatment Options

- **Switch** from one type of estrogen to another (e.g., Premarin, conjugated equine estrogen, most commonly used preWHI, may increase headache)
- **Change the formulation**; consider combination patch
- **Increase or decrease** the dosage
- Change the **route** of administration
- Consider **adjunctive** therapy
- **Cessation** of therapy

Polly

- 47 year old woman with severe menstrually related migraine
- Real estate broker
- Regular menstrual periods
- Brain “fog” during presentations
- Sleepless, moody, anxious
- FSH high

Polly

- What to do?
- Full medical evaluation - exclude pregnancy (2nd highest rate of unplanned pregnancies
- Screen for diabetes, thyroid dysfunction, breast, cervical, and colon cancer, Htn, cholesterol, vascular risks, bone disease
- Assess treatment options

Migraine Pregnancy Registries

- Lasmiditan: www.migrainepregnancyregistry.com 833-464-4724
- Rimegepant: Migraine Observational Nurtec Pregnancy Registry (MONITOR) 877-366-0324
- Erenumab: Genesis Pregnancy Registry 833-244-4083
- Fremanezumab: Teva Migraine Pregnancy Registry 833-927-2605
- Galcanezumab: PASS www.migrainepregnancyregistry.com 833-464-4724

- PUSH FOR PATIENTS TO REGISTER and BE FOLLOWED!!!

Hormonal Treatment Options

Around time of migraine

Use an estrogen/progesterone patch

Add estrogen patch to her progestin intrauterine device -monitoring endometrium

If contraception is needed

Consider newer lower dose combined oral contraceptive

If contraception not needed

Change to an estrogen/progesterone patch or gel

If older and no perimenopausal symptoms, other than migraine

Simply discontinue all hormonal therapies and treat symptomatically

Polly Assessed for Management of Migraine and Perimenopause

- Hormonal Options
  continuous or cyclic fixed dose
- Low dose birth control pills
- HRT: pill, patch, ring
- Alternative Approaches
- Nutrition/Exercise
  Black cohash/dong quai/phytoestrogens
  Exercise
- Standard therapy
  Acute, short term and/or daily preventive tx

Polly's Choices

- Continuous birth control pill use for nine week intervals
- Every ninth week, estrogen dot during placebo week, and suma/naproxen fixed dose tablet for breakthrough attacks
- Weight bearing exercise, sleep hygiene
- Similar approaches to menstrual migraine

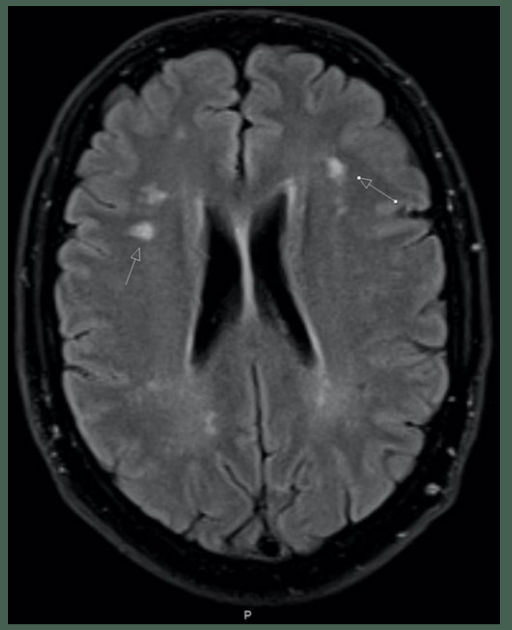
Had Polly Failed OCPs..

- With continued regular menstrual cycles
- Low dose estrogen patch may be offered continuously
- WHI/HERS controversy:
  - specific formulation
  - older women
  - multiple risk factors
- Comorbidities benefit:
  - mood disorders
  - sleep disturbances
  - bone health
- Keep in mind, hypoestrogenized women appear most at risk

Polly at Menopause

- No menstrual periods for 18 months
- Transition to estrogen/progesterone patch with family hx for osteoporosis
- Plan to continue for three to five years, with gradual complete taper

Pathophysiology of Disease Progression



- Migraine sufferers have more MRI-detectable white matter lesions than controls. White matter lesions increase with attack frequency, possibly demonstrating progression
- Kruit et al's cross sectional study of population-based sample of Dutch adults ages 30-60 years
- Results: Some patients with migraine ***with or without aura*** are at an increased risk for ***subclinical lesions*** in certain brain areas

- Increased risk of posterior circulation infarcts highest in migraineurs with aura with an attack frequency >1/month
- Increased risk of deep white matter lesions highest in female migraineurs (with or without aura) with an attack frequency ≥1/month

As few as one headache per month could predispose migraineurs to subclinical brain lesions.

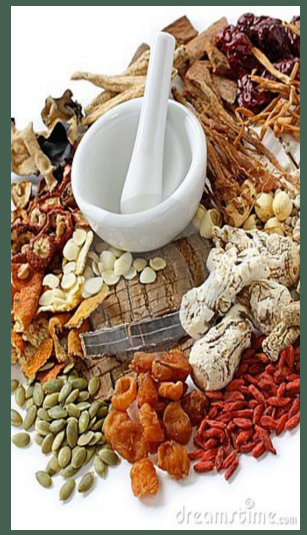
Kruit MC et al. *JAMA*. 2004;291:427-434.

Open Label Studies

- Tamoxifen
- Danazol
- Combination of phytoestrogens
- Exception: 60mg soy isoflavones
  100mg dong quai
  50mg black cohash
- Combination showed some reduction in 49 women, but precludes studying single effect

Folk Remedies for Perimenopausal Symptoms

- Bee pollen
  - Combination of "male and female" hormones
    - Dose: 3 Bee pollen pills (500 mg) a day
- Grated nutmeg
  - Mix 1 ounce of grated nutmeg in 1 pint of Jamaican rum
    - Dose: 2 tsp TID
- Cucumber
  - Contains "beneficial" hormones



Diagnosis and Management Of Headache in Perimenopause and Menopause

- Take the history!
- In age-appropriate women presenting with HA, always ask about "menopausal" symptoms
- Establish link, if exists, between any hormonal tx, whether HRT or OCP, and headache
- Identify stroke/cardiac/thromboembolic risk factors and treat early
- Encourage three month diaries
- Consider hormonal based therapies, if appropriate; goal is stabilization of estrogen levels

Disclosures

- Eli Lilly/Syneos
- National Headache Foundation

THE END