



Doc, It's My Hormones!

Female Sex Hormones and Common

Complaints

Mitra A. Razzaghi, MD

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"WISH"

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Female Sex Hormone related medical complaints

- ❖ PMDD/PMS
- ❖ Migraine headaches
- ❖ Weight issues
- ❖ Thyroid issues
- ❖ Skin and hair issues

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**I AM THE WARRIOR
I DON'T HAVE PMS**



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PMDD aka Luteal Phase Dysphoric Disorder

- ❖ Cyclic physical and/or behavioral symptoms
- ❖ Over 100 symptoms ascribed, 20 confirmed
- ❖ Symptoms of anger, irritability and internal tension severe enough to interfere with the woman's life
- ❖ Major Sx: Fatigue, Abdominal bloating, Anxiety, Emotional lability, breast tenderness and headache
- ❖ Other symptoms: dizziness, weight gain, joint or muscle pain, sleep difficulties, appetite change, trouble concentrating, hot flashes, heart palpitations

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Frequency of Symptoms of PMS

Symptom	Frequency: percent of cycles
Fatigue	92
Irritability	91
Bloating	90
Anxiety/Tension	89
Breast tenderness	85
Mood liability	81
Depression	80
Food cravings	78
Acne	71
Increased appetite	70
Oversensitivity	69
Swelling	67
Expressed anger	67
Crying easily	65



Epidemiology

- ❖ PMS: mild 75%, clinically significant 20-30%
- ❖ PMDD 3-8%
- ❖ PMDD overestimated because of the failure to apply strict inclusion criteria
- ❖ Disparity between different ethnic/cultural background
 - Smaller percentage described in diverse cultural settings
 - Blacks vs. Whites 2.9:4 percent



Risk Factors

❖ Genetic factors

- Strong correlation with FH of PMDD and PMS
- No correlation with inheritance of other mood disorders
- Genetic variation in ESR1 (estrogen receptor alpha) gene

❖ Lower education

❖ Smoking

❖ High "Daily Hassle Score"

❖ History of traumatic event or anxiety

7 disorder



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Pathogenesis

❖ Gonadal steroids

- Comparable concentration of E2 and P in patients with PMS/PMDD with asymptomatic control
- Progesterone receptor antagonist (Mifepristone or ru486) does not alleviate symptoms
- Possible mechanism: abnormal response to normal hormonal changes

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Pathogenesis

❖ Neurotransmitters:

- Cyclic fluctuations in circulating estrogen and progesterone cause marked changes in the **opioid, GABA and serotonin systems**
- Also changes **peripheral beta-endorphin** levels
- **Serotonin depletion** plays major player
 - Symptoms of PMS are ameliorated by the serotonin agonist Fenfluramine and aggravated by acute depletion of the serotonin precursor tryptophan
 - Administration of Metergoline, a serotonin antagonist, to fluoxetine-treated women with PMDD causes a return of mood symptoms



Pathogenesis

❖ Vitamins and nutrients

- No differences in serum vitamin E, vitamin A, or vitamin B6 levels in patients and controls or during cycle
- High intakes of the dietary **thiamine and riboflavin** -> less likely to develop PMS
- Treatment with vitamin **B6 100mg/day** was reported to be more effective than placebo
- Improvement in total PMS symptom scores and affective symptoms with the administration of **magnesium** pyrrolidone carboxylic acid (360 mg three times daily in the second half of the menstrual cycle)



Diagnosis

❖ 40% of women presenting with presumed PMDD, have other diagnosis commonly mood or anxiety disorders

❖ Diagnostic Criteria

- The specific symptom
- Timing of symptoms related to luteal phase
- Severity of symptoms
- Absence of hormone or drug ingestion, exclusion of other diagnoses



Diagnosis

- ❖ The DSM-IV criteria for diagnosing PMDD:
Prospective documentation of physical and behavioral symptoms (using diaries) being present for most of the preceding year.
 - Five or more of the symptoms must have been present during the week prior to menses
 - Resolving within a few days after menses starts
 - At least one of the five symptoms must be one of the first four on list
 - A valid and reliable prospective symptom inventory is required to make the diagnosis of PMDD e. g. Calendar of Premenstrual Experiences (COPE)



Diagnosis

- ❖ Diagnostic criteria DSM –IV qualifying symptoms
 - 1- **Feeling sad, hopeless, or self-deprecating**
 - 2- **Feeling tense, anxious, or "on edge"**
 - 3- **Marked lability of mood interspersed with frequent tearfulness**
 - 4- **Persistent irritability, anger, and increased interpersonal conflicts**
 - 5- Decreased interest in usual activities, which may be associated with withdrawal from social relationships
 - 6- Difficulty concentrating
 - 7- Feeling fatigued, lethargic, or lacking in energy
 - 8- Marked changes in appetite, which may be associated with binge eating or craving certain foods
 - 9- Hypersomnia or insomnia
 - 10- A subjective feeling of being overwhelmed or out of control
 - 11- Other physical symptoms: breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, weight gain



Diagnosis

☒ COPE: Calendar Of Premenstrual Experiences

- 10 most commonly reported physical symptom
- 12 most commonly reported behavioral symptoms
- Sx rated daily throughout the menstrual cycle
- Total score <40 during days 3 to 9 of the menstrual cycle AND a >42 during the last 7 days of the menstrual cycle is diagnostic

☒ Validity

- high degree of correlation between COPE scores and the Profile of Mood States and the Beck Depression Inventory



Premenstrual Daily Symptoms Diary



Name: _____ Month: _____

Write the date in the first row, starting with today. Circle the days of your menstrual period.

Each day, rate the severity of your symptoms: 1= no symptoms, 2 = mild symptoms,

3 = moderate symptoms, 4 = severe symptoms

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Irritability & tension																															
Anger & short temper																															
Anxiety & nervousness																															
Depression & sadness																															
Crying & tearfulness																															
Relationship problems																															
Tiredness & lack of energy																															
Insomnia																															
Changes in sexual interest																															
Food cravings & overeating																															
Feeling overwhelmed																															
Headaches																															
Breast tenderness & swelling																															
Back pain																															
Abdominal pain																															
Weight gain																															
Nausea																															
Other (specify)																															
Other (specify)																															



Diagnosis

✦ UCSD for PMS:

- at least one of 6 behavioral symptoms: fatigue, irritability, depression, expressed anger, poor concentration, and social withdrawal
- at least one of 4 somatic symptoms: breast tenderness, abdominal bloating, headache, or swollen extremities
- at least **one behavioral symptom** and **one physical symptom** within five days of the onset of menses in two consecutive cycles
- a characteristic **symptom-free interval from cycle days 4 through 12** of the idealized 28 day menstrual cycle



Diagnosis

- ❖ A variety of medical disorders (e.g., migraine, chronic fatigue syndrome, irritable bowel syndrome) are exacerbated just prior to or during menses
- ❖ History, physical examination, chemistry profile, complete blood count, and serum TSH
- ❖ Irregularity of menstrual cycles needs gynecologic endocrine evaluation
- ❖ Record symptoms prospectively for two months
- ❖ If no symptom free interval in the follicular phase, patient should be evaluated for a mood or anxiety disorder



Treatment

❖ Non-pharmaceutical

- Regular exercise
- Relaxation therapy
- Avoidance of excess salt and large meals
- NSAIDs
- Chaste Berry 200 mg/day
- Vit B6 100mg/day
- Bright light therapy





Treatment of PMS with Vitex Agnus Castus Extract “Chaste Berry”

	Active n=86	Placebo n=84	Difference in mean	P value
Irritability	-28.9	-18.2	-10.7	0.001
Mood alteration	-28.7	-17.6	-11.1	0.001
Anger	-22.1	-11.7	-10.3	0.001
Headache	-17.8	-5.9	-11.9	0.001
Bloating	-12.4	-13.7	1.3	NS
Breast fullness	-18.6	-9.4	-9.2	0.001
Responder rate	52	24		

Schellenberg BMJ 2001;322:134



Treatment

❖ Alprazolam

- Alprazolam (0.25 mg three or four times daily) beneficial in double-blind, placebo-controlled crossover studies

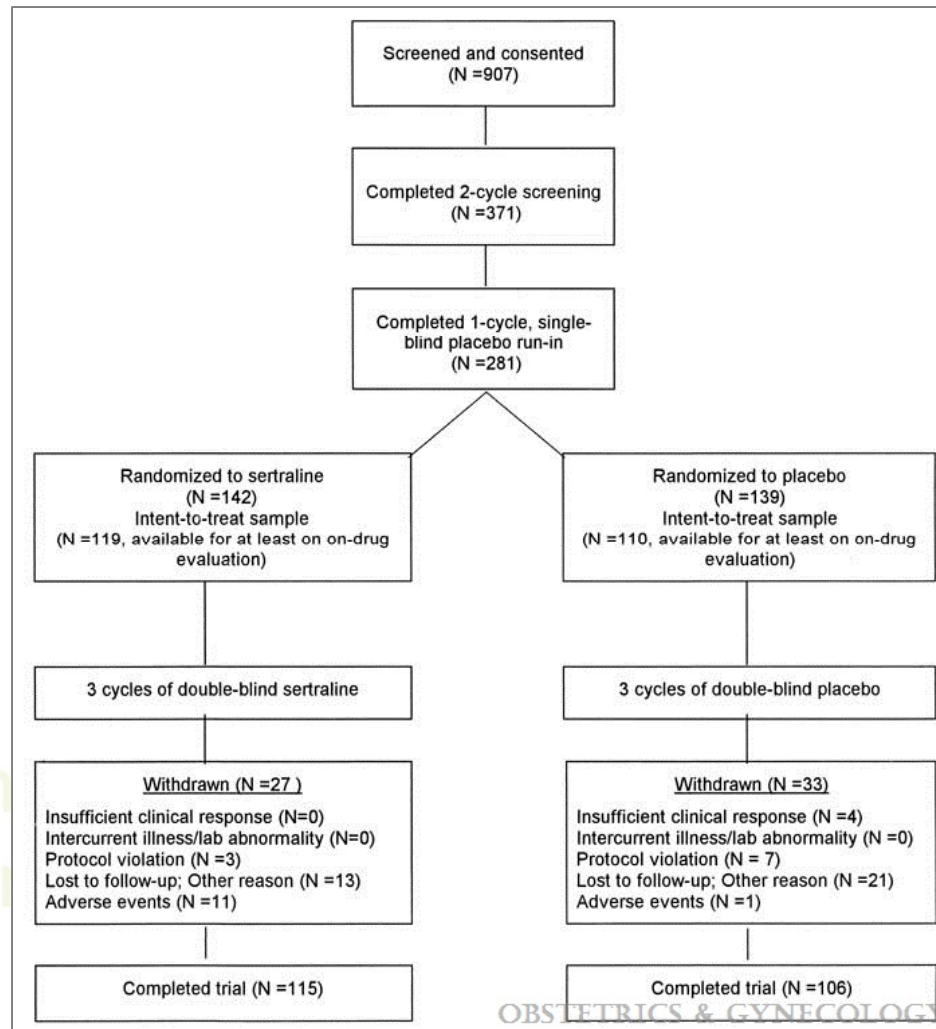
❖ Luteal phase therapy with SSRI

- SSRI on second half of cycle 70-85% response
- Intermittent therapy starting on cycle day 14-21 to few days after menses for affective symptoms
- Higher doses of the SSRI needed in some women to adequately treat physical symptoms

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Luteal Sertraline in PMDD



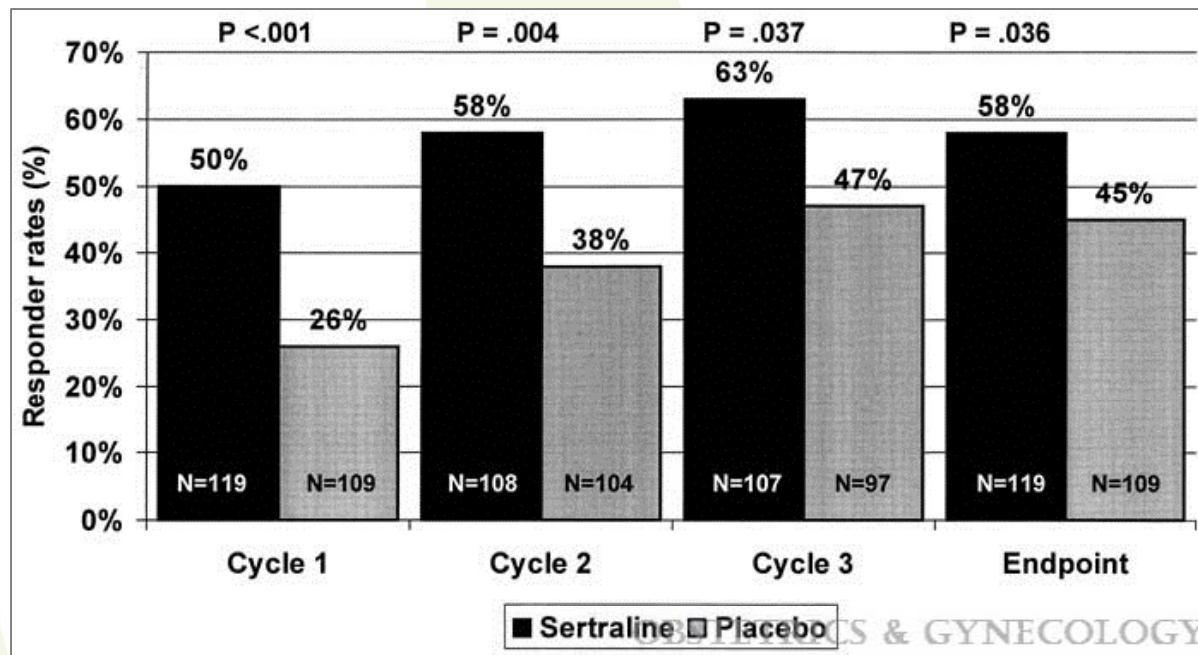
OBSTETRICS & GYNECOLOGY

Halbreich. Luteal Sertraline in PMDD. Obstet Gynecol 2002

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Luteal Sertraline in PMDD



Halbreich. Luteal Sertraline in PMDD. Obstet Gynecol 2002



Treatment

- ❖ OC not better than placebo for treatment of PMS
- ❖ Continuous OC's, or OC's such as Yaz (20 mcg E2 and 3 mg Drospirenone) shorter placebo interval are effective in some
 - Possible increased risk of VTE with Drospirenone troublesome
 - On Dec 2011 FDA panel voted the benefits of the preparation outweighs risks but recommended better labeling to reflect potential for VTE.
- ❖ Cochrane Systematic Review 2009 conclusion:
 - Placebo has large effect
 - Drospirenone + E2 20 mcg (Yaz) may help treat PMDD



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Treatment

Danazol

- Inhibits pituitary gonadotropin secretion
- Very effective in treatment of PMS
- The androgenic side effects of Danazol limits its use to patients who fail to respond adequately to the above therapies.

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Treatment

❖ Ineffective treatments

- progesterone
- tricyclic antidepressants and monoamine oxidase inhibitors
- lithium
- several popular dietary supplements including
 - Evening primrose oil
 - Essential free fatty acids
 - Ginkgo Biloba



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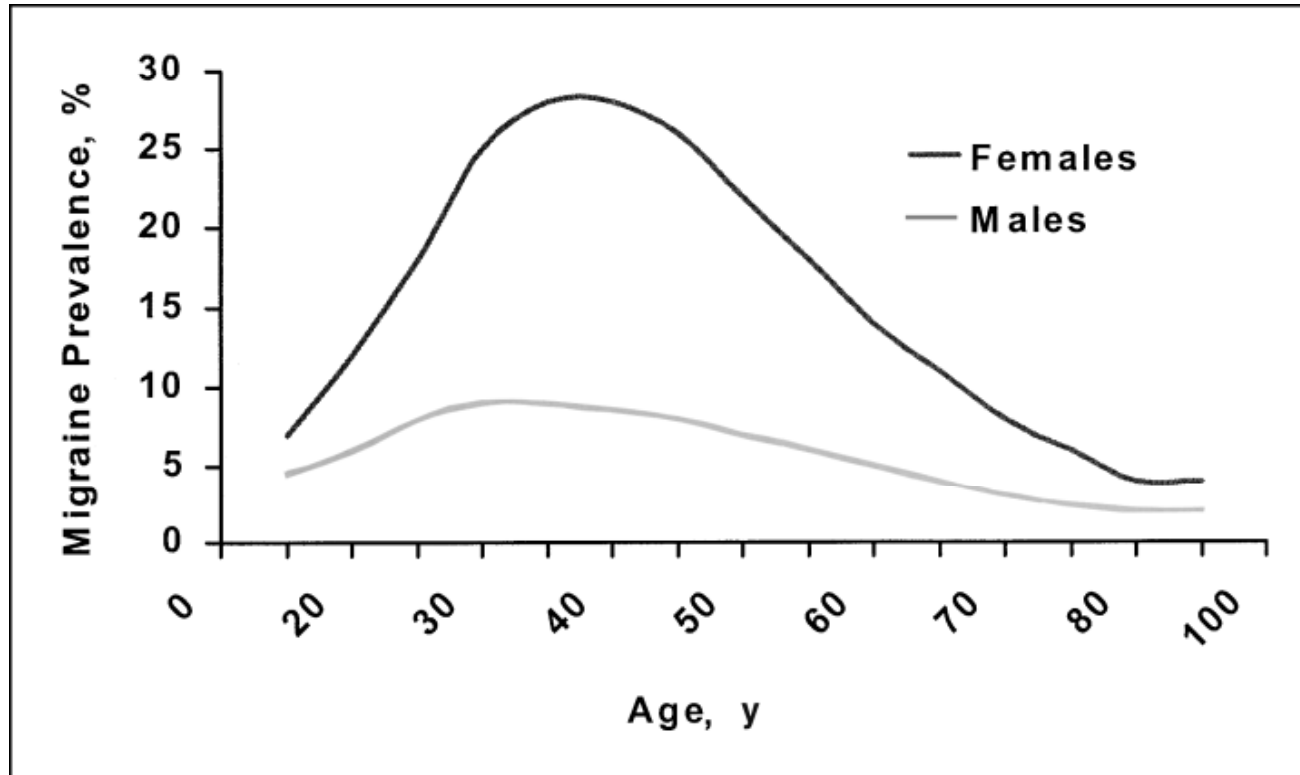
Estrogen Associated Migraine



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Prevalence and Burden of Migraine in the United States: Data From the American Migraine Study II

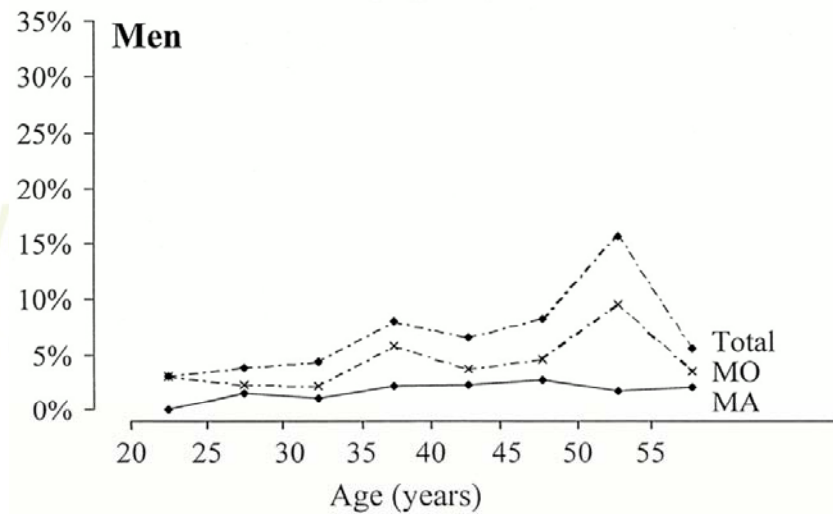
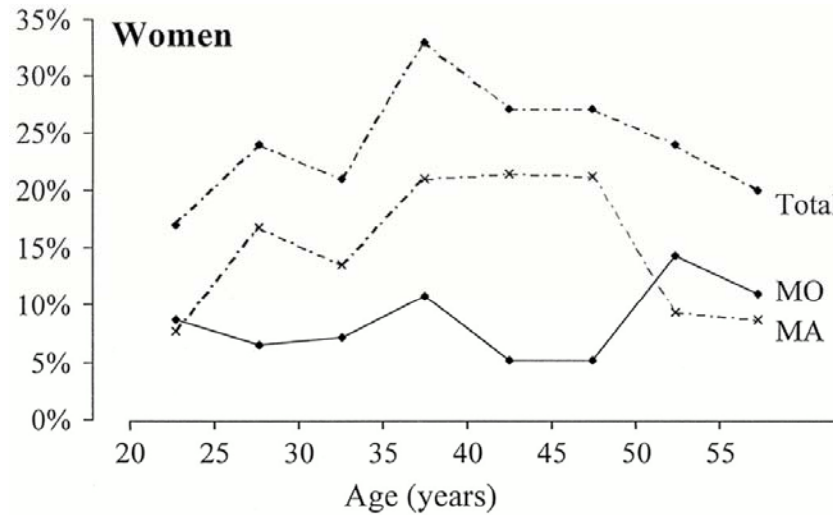


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Launer L J et al. Neurology 1999;53:537-537



One-year prevalence ratio of migraine and subtypes by age.



Launer L J et al. Neurology 1999;53:537-537



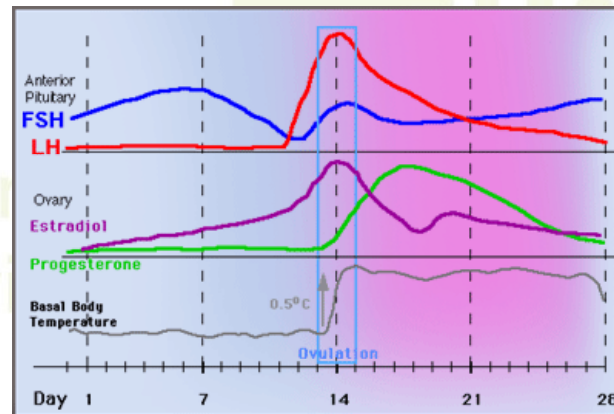
Estrogen Associated Migraine

- ❖ Migraine 3 times more prevalent in women
- ❖ Pure menstrual headache
 - 2 days before to 3 day into period in 2/3 of cycles
- ❖ Menstrual related migraines
 - Both menstrual and non-menstrual
 - Worse symptoms around menstruation

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Pathophysiology

- ❏ Trigger: Decline in estrogen concentration after priming
 - Natural: start of menses, postpartum
 - Scheduled withdrawal from exogenous E2
 - Unintentional E2 withdrawal (med interaction)





Pathophysiology

Estrogen effect on CNS

- Facilitation of **serotonergic** and **glutamatergic** systems
- Fall In E2 level causes fall in serotonin
- Release of **calcitonin gene-related peptide** and **substance P** from trigeminal nerves
- Vasodilation of cranial vessels, sensitization of meningeal afferents of trigeminal nerves
- Effect on NO, Mg, Prostaglandins that modulate neurotransmission balance

JAMA. 2006;295(15):1824

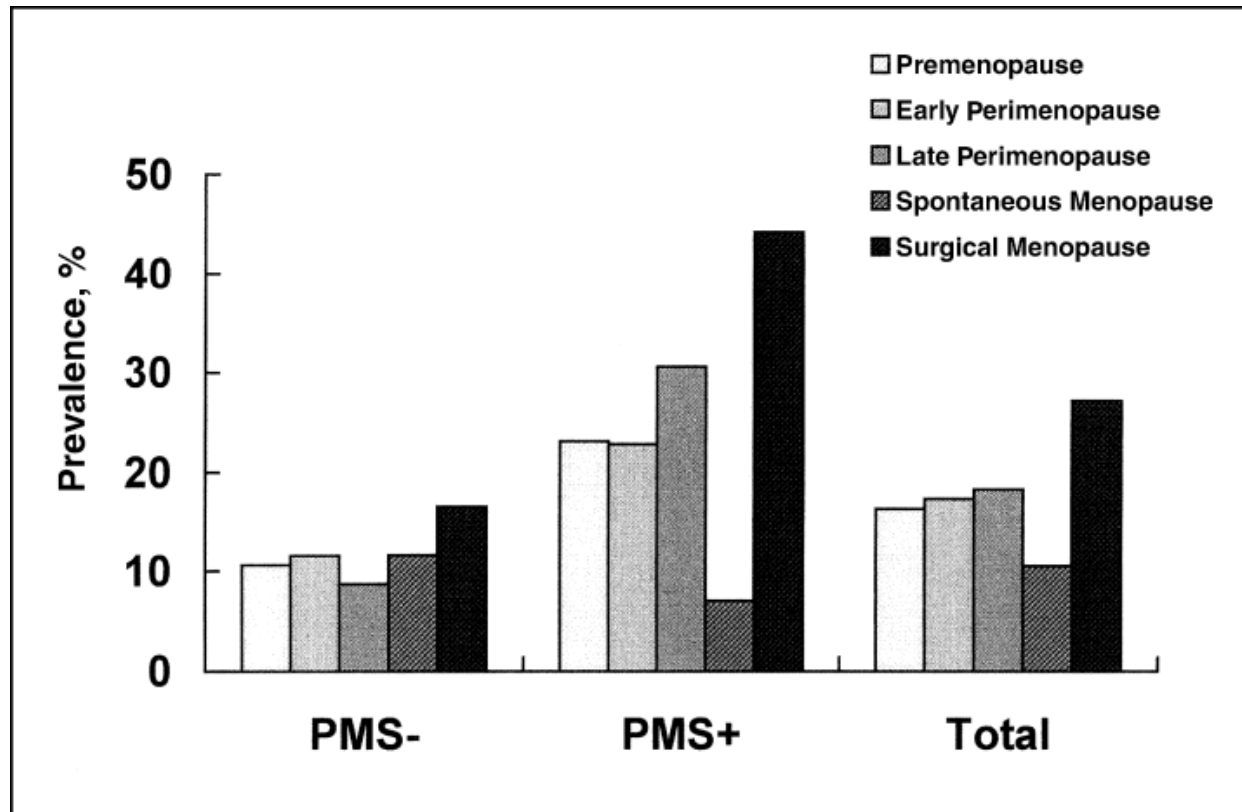


Epidemiology

- ❖ Increased incidence in girls with onset of puberty
- ❖ Common in perimenopausal period, peak early 40's
- ❖ Migraine up to 41% of women by age 50, fall by half after menopause.
 - Chronic daily headaches worsen initially
- ❖ High incidence of chronic migraine in patients with endometriosis



Migraine association with PMS



Headache: The Journal of Head and Face Pain 470-478, 2003



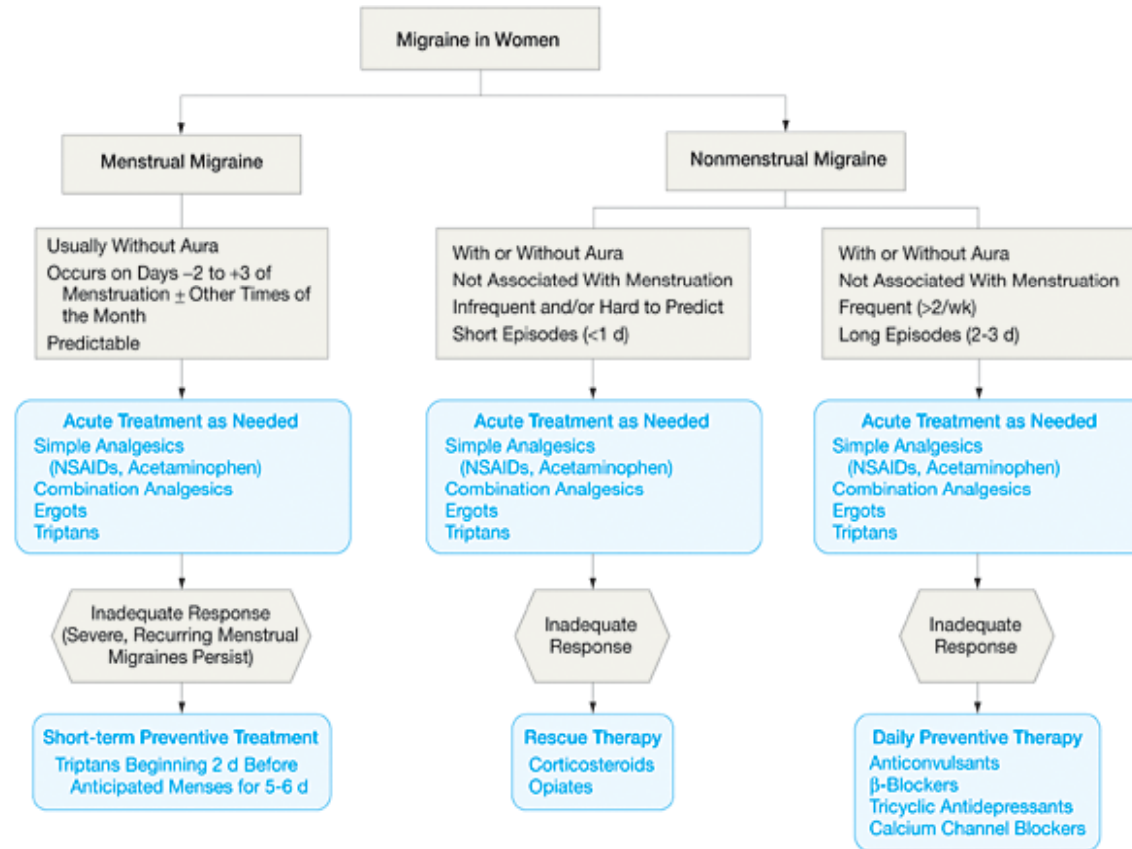
Characteristics

- ❖ Menstrual migraines are more severe, last longer, less responsive to acute treatment
- ❖ Usually not associated with aura due to relatively low estrogen environment with menses
- ❖ Pure menstrual migraine less common than menstrual related (21% vs. 56%)

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Treatment Algorithm for Migraine in Women



Brandes, J. L. JAMA 2006;295:1824-1830



Treatment

☒ Abortive:

- Fast-acting triptan early in mild pain stage
 - Study with Sumatriptan 50% complete response, 42% severity decreased by 50%
- NSAID such as Mefenamic acid 500 TID
- Combined Triptan and NSAID
- Positive studies with long acting triptans:
 - Naratriptan (Amerge, half-life 6h, 1-2.5 mg/dose, max dose 5mg/day)
 - Frovatriptan (Frova half-life 26h, 2.5 mg/dose, max 7.5mg/day)



Treatment

❖ Preventive treatment

- Magnesium 120mg TID x 2 wks starting day 15th of cycle
 - Small DBPC study in Italy, over 50% response after 3 months. Effect decreased with open study in the same group
- Extended-cycle E/P combined contraceptives
- Cyclic E/P contraception with supplemental estrogen
- Natural cycles with supplemental estrogen
- Non-hormonal therapy: long-acting triptan BID

Headache. 2009; 31(5):298



Estrogen Based Therapies

- ❖ Peri-menstrual transdermal E2 patch/gel for a week
 - Estradiol Patch 0.1 mg/24 hr, or Estradiol gel 1-1.5 g/d just before period
 - Timing is very important – starting too early or stopping too soon can cause HA
- ❖ SERM, GnRH agonists and progestins not safe or effective

Neurology. 2008; 70(17):1555 and 2006; 67(12):2159



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Peri-menopause Migraines

- ❖ 3-7 year prior to menopause
- ❖ Menstrual irregularities and vasomotor symptoms
- ❖ Increase in migraine headaches and chronic daily headaches
- ❖ After menopause, migraines improve but CDH do not due to sleep and mood disruptions



Migraine and stroke

- ❖ Data from observational studies: migraine may be a risk factor in developing stroke
- ❖ Women with migraine with aura: up to 2-fold risk of ischemic stroke
 - Risk higher in smokers and OCP users
- ❖ No increased risk of myocardial infarction

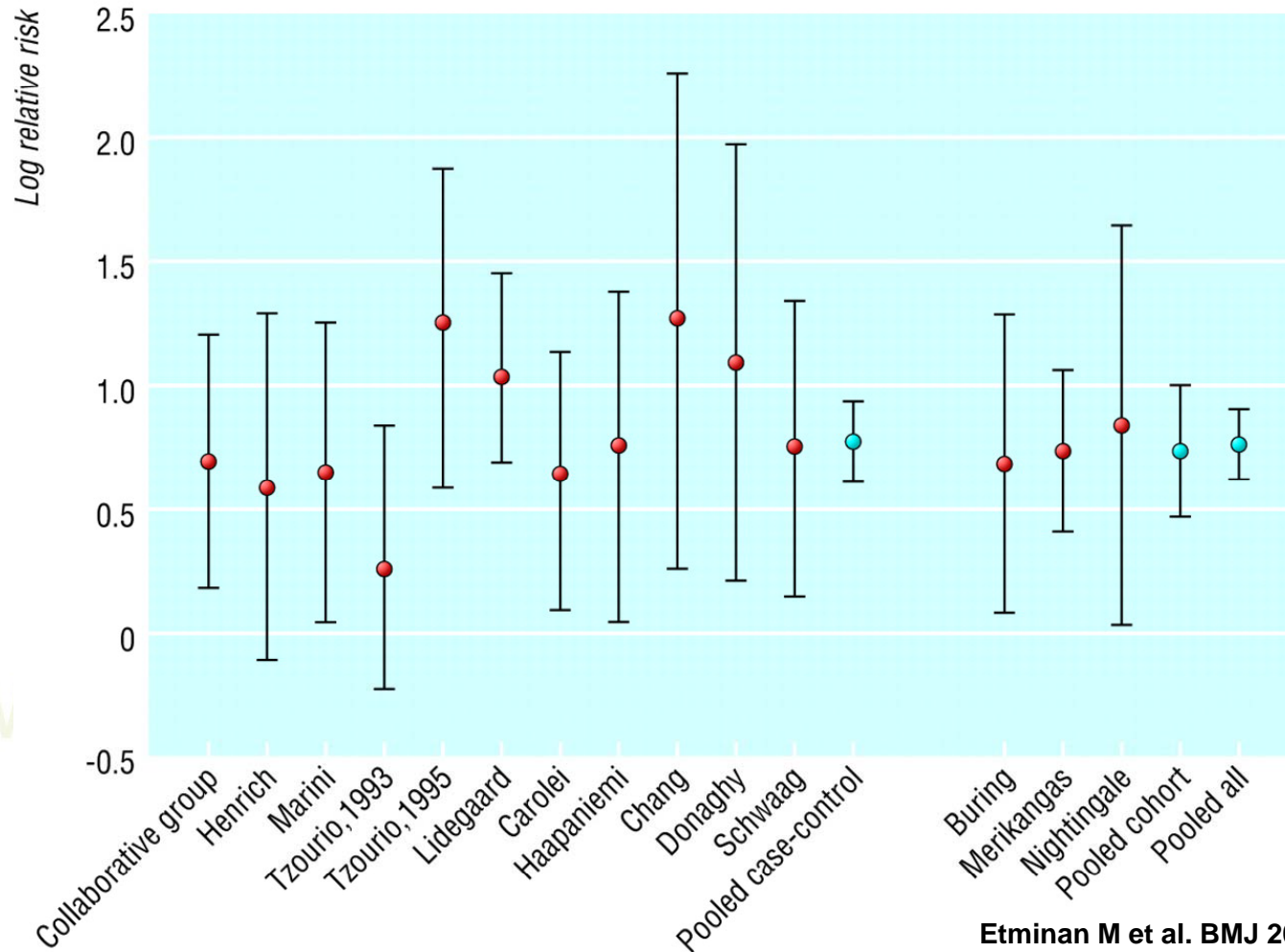
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Schurks, BMJ. 2009;339:b3914

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Forest plot of the studies of migraine and ischaemic stroke



Etminan M et al. BMJ 2005;330:63



Contraception and migraine

- ❖ Women with migraine without aura
 - Low dose OCP (<50mcg E2) acceptable if no other risk factors
- ❖ Women with migraine with aura
 - No OCP
 - Barrier methods, surgical methods if not desiring pregnancy, IUDs including Mirena IUD

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Table 3. Summary of Guidelines for the Use of Combination Estrogen–Progestin Oral Contraceptives in Women with Characteristics That Might Increase the Risk of Adverse Effects.*

Variable	ACOG Guidelines	WHO Guidelines
Smoker, >35 yr of age <15 cigarettes/day ≥15 cigarettes/day	Risk unacceptable Risk unacceptable	Risk usually outweighs benefit Risk unacceptable
Hypertension Blood pressure controlled	Risk acceptable; no definition of blood-pressure control	Risk usually outweighs benefit if systolic blood pressure is 140–159 mm Hg and diastolic blood pressure is 90–99 mm Hg
Blood pressure uncontrolled	Risk unacceptable; no definition of uncontrolled blood pressure	Risk unacceptable if systolic blood pressure is ≥160 mm Hg or diastolic blood pressure is ≥100 mm Hg
History of stroke, ischemic heart disease, or venous thromboembolism	Risk unacceptable	Risk unacceptable
Diabetes	Risk acceptable if no other cardiovascular risk factors and no end-organ damage	Benefit outweighs risk if no end-organ damage and diabetes is of ≤20 yr duration
Hypercholesterolemia	Risk acceptable if LDL cholesterol <160 mg/dl and no other cardiovascular risk factors	Benefit–risk ratio is dependent on the presence or absence of other cardiovascular risk factors
Multiple cardiovascular risk factors	Not addressed	Risk usually outweighs benefit or risk unacceptable, depending on risk factors
Migraine headache Age ≥35 yr Focal symptoms	Risk usually outweighs benefit Risk unacceptable	Risk usually outweighs benefit Risk unacceptable
Breast cancer Current disease Past disease, no active disease for 5 yr Family history of breast or ovarian cancer	Risk unacceptable Risk unacceptable Risk acceptable	Risk unacceptable Risk usually outweighs benefit Risk acceptable

Petitti, NEJM 2003; 349:1443-1450

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