Women’s Issues 2013

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Disclosures

- Consultant: Allergan, MAP, Merck, Nautilus, Zogenix

- Research Support: ElectroCore, GlaxoSmithKline

- Speakers Bureau: Nautilus, Zogenix

- I will use brand-names when discussing hormonal contraceptives due to unwieldy generic nomenclature
  - I have no financial relationship with any of these products
Ask Anne

Hormonal Advice
(with apologies to Ann Landers....)
Ask Siri
“Siri, what’s wrong with me?”

Now look here, Marsha. You’re good enough, you’re smart enough, and doggone it, people like you.
Inherited threshold for trigeminal activation

Triggers or stressors

Episodic Migraine

Non-restorative sleep

Medication overuse

Anxiety

Chronic Migraine

“Siri, the blue pill or the white one?”

“Either way... I’ll still be here when you wake up.”
Hormonal Contraceptives in Prevention of Menstrual Migraine

- The goal is to limit the drop in estrogen that triggers MRM
  - Inhibit ovulation (thereby control estrogen exposure and eliminate cycling)
  - Limit any declines in estrogen to ≤10μg EE
- Progestin-only options typically do not inhibit ovulation
- Very low-dose pills (≤25μg EE) may not inhibit ovulation
  - Inhibition of ovulation is not necessary to prevent pregnancy
  - With very low-dose pills, ovulation is more reliably inhibited with a shorter “PFI” (pill-free interval)
No hormonal contraceptive (or estrogen therapy) is indicated for the prevention of menstrual migraine
The “Architecture” of OCs (Estrogen Component Only)

Natural cycle

decline ≈ 20 μg EE equivalent
The “Architecture” of OCs (Estrogen Component Only)

- **Natural cycle**
  - Decline ≈ 20 µg EE equivalent

- **EE triphasic**
  - 30 µg EE decline

- **100 µg**
  - 100 µg EE decline

- **50 µg**
  - 50 µg EE decline

- **35 µg**
  - 35 µg EE decline

- **Extended cycle, 20 µg / 10 µg in week 13**
  - 20 µg EE decline

- **Extended cycle, 30 µg / placebo in week 13**
  - 30 µg EE decline

- **Continuous, 20 µg**
  - No longer available in the US

- **No longer available in the US**

- **“Stepped EE”**
  - 35 µg EE decline

- **20 µg / 0 / 10 µg**
  - 20 µg EE decline

- **“High Dose OC”**
  - 30 µg EE decline

- **No decline**

- **Decline ≈ 20 µg EE equivalent**

The “Architecture” of OCs (Estrogen Component Only)
Ethinyl estradiol; norethindrone acetate 1.5/30
Ethinyl estradiol; norethindrone acetate 1/20
Ethinyl estradiol;
norethindrone acetate 1/10
Extended cycle, 20 µg / 10 µg in week 13
10 µg EE decline

DIY versions* can be made using Mircette, Kariva, Azurette, or other generics with 20/0/10 format

*The progestin in these DIYs is desogestrel, as opposed to levonorgestrel in LoSeasonique

Save the last 5 pills. Take 7 of them nightly in week #13.
DIY versions can be made using any monophasic combined hormonal contraceptive in an “active pills only” regimen.

Caution is advised with concomitant use of topiramate, particularly at high doses:

- Topiramate increases the rate of estrogen metabolism 38%, resulting in exaggerated daily declines.
- Vaginal ring or patch formulations are better options in these instances.
“Siri, there was a dyslexic, an agnostic, and an insomniac. Which one stayed up all night wondering if there was a dog?”

“What???”

“OK, would you like me to search for ‘dog’?”
15–year prospective population–based study examined risk of MI and stroke in healthy CHC users
- 1,626,158 women aged 15–49 (14,251,063 person–years of observation)
- 3,311 thrombotic strokes and 1,725 MIs occurred

Overall risk for stroke and MI is small
- 21.4/100,000 person–years for stroke
- 10.1/100,000 person–years for MI

Absolute risk of thrombotic stroke and MI was *not* significantly increased with CHCs containing 20μg EE (very low dose)

Risk was increased (1.4–2.2) with 30–40μg EE pills

The progestin dose had no influence on these endpoints

Data from a cohort of >800,000 CHC users were analyzed.

3 formulations were compared to OCs containing 20μg EE:

- Oral drospirenone 3.0/30μg EE
- Transdermal patch (6.0 mg norelgestromin/0.75 mg EE; delivers 20 μg EE/24 hrs)
- Vaginal ring (11.7 mg etonogestrol/2.7 mg EE; delivers 15 μg EE/24 hrs)

Compared to 20μg EE pills, there was increased risk for stroke and MI only with the 30μg EE/drospirenone-containing pills (RR 2.01 [1.01–3.81])

- Highest risk was in the older cohort, ages 35–55 years

No significant risks were seen with the other preparations

Sidney S, Cheetham T, Connell hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. Contraception 2012;87:93–100.
“Siri, are you ovulating?”

“No comment, [CENSORED]"


Means with SE for 102 patients
- 21/7 cycle
# Headache Calendars

(No hormonal medication)

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| xxx | xxx | xxx |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

15 severe, 7 moderate, 6 mild
HA index = 65

### Post-treatment:  No hormonal medication

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1 severe, 2 moderate, 3 mild
HA index = 7
# Headache Calendars

**Levonorgestrel + estradiol 0.1, changed q Wednesday**

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9 severe, 18 moderate, 1 mild

**HA index = 64**

**Post-treatment: levonorgestrel + ethinyl estradiol**

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0 severe, 6 moderate, 7 mild

**HA index = 19**
Headache Calendars
(no hormonal medications)

| S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S |
| xx | x | xx | xx | x | x | xx | xx | xx | x | xx | xx | xx | x | xx | xx | xx | x | xx | xx | xx | xx | xx | xx | xx | xx | xx | xx |

7 severe, 12 moderate, 1 mild
3 auras/month
HA index = 46

Post-treatment: Ethinyl estradiol/etonogestrel APO

| S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S |
| x | xx | xx | xx | xx | x | o | o | o | x | xx |

0 severe, 2 moderate, 4 mild
(1 aura in past 2½ months)
HA index = 14
Meds:
Ethynyl estradiol; norethindrone acetate FE 1/20 hs
Sumatriptan 100 mg 14/mon
Naproxen 20/mon
Benadryl 50mg hs 10x/mon

Caffeine:
One “grande” of Starbucks + one can of soda/day

Works irregular shifts, with one 10-hr, one 15-hr and one 24-hr shift each week.

45 yr old neonatal NP with chronic migraine and MRM
Worst migraine is a 4-6 day severe MRM that begins one day before the onset of bleeding. Also reports a consistent 3-4 day ovulatory migraine on Loestrin 1/20.

Other triggers:
- Inadequate Sleep
- Fasting
- Stress
- Weather

Vital Signs:
- Ht: 65 inches
- Wt: 280 pounds
- BP: 138/90
- Pulse: 81
Baseline Headache Calendar

Ethinyl estradiol; norethindrone acetate FE 1/20

| S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S |
| XX | x | x | xx | x | xx | xx | xx | x | x | x | xx | x | x | x | xx | x | xx | x | x | x | xx | xx |
| x | xx | xx | xx | x | xx | xx | xx | x | x | x | xx | x | x | x | xx | x | xx | x | x | x | xx | oo |
| oo | xx | xx | xx | x | xx | xx | xx | x | x | x | xx | x | x | x | xx | x | xx | x | x | x | xx | oo |
| xx | xx | xx | xx | x | xx | xx | xx | x | x | x | xx | x | x | x | xx | x | xx | x | x | x | xx | oo |

6 severe, 8 moderate, 11 mild
HA index = 51
SLEEP HISTORY:

- On “days,” gets in bed at 11:00 PM, reads for 15 minutes, then falls asleep quickly.

- Gets up 3x/night to urinate. Supper is at 8:00 PM; drinks 16-20 oz water after supper.

- Arises “OK” at 6:20 AM. Takes weekly naps and sleeps 1.5 hrs later on weekends.
TREATMENT OVERVIEW:

- Sleep hygiene
  - Note for straight day shifts at work
  - Move supper ≥4 hrs before bedtime
  - Decrease fluids to ≤6 oz in the 2 hrs before bedtime
Sleep Stages
TREATMENT OVERVIEW:

- Sleep hygiene, treat PLMS
- Rotate acute medications
- Taper off caffeine
“Siri, everytime I drink coffee, I get a stabbing pain in my right eye.”

“Have you tried taking the stirrer out of the cup first?”
Tall = 12 oz
Grande = 16 oz
Venti = 24 oz
Trenta = 31 oz

Reference “cup” of coffee = 6 oz.
Average mug = 12 oz.
Average to go serving = 20 oz.
Caffeine Content

Starbucks coffee (16 oz)

Generic coffee (16 oz)

Brewed tea (16 oz)

Red Bull (8.3 oz)

Excedrin (1 tablet)

Diet Coke (12 oz)

Decaff coffee (16 oz); Hot cocoa (8 oz); Hershey bar (1.5 oz)
ADENOSINE & HEADACHES

Acute vs. Chronic Caffeine Exposure

- Adenosine is a purine nucleotide generated from ATP\(^1\)
  - Astrocytes are the primary source of adenosine in the brain
- Actions of adenosine\(^2\)
  - Fatigue, drowsiness
  - Diffuse, dull pain
  - Vasodilation in CNS, not peripherally
  - Reduces neuronal firing rate and cortical excitability
- Plasma adenosine increases during migraine attacks \(^3\)
- Exogenous adenosine triggers migraines \(^4\)
- Dipyridamole (adenosine reuptake inhibitor) increases migraine attack frequency \(^5\)
- CNS adenosine levels increase during prolonged wakefulness and decrease during prolonged sleep

ADENOSINE & CAFFEINE

- Caffeine is a competitive antagonist of adenosine
- Consumption of caffeine increases activity of
  - Epinephrine
  - Norepinephrine
  - Glutamate
  - Cortisol
  - Acetylcholine
  - Dopamine
  - Serotonin
- Administration of caffeine leads to cerebral vasoconstriction and a compensatory increase in plasma adenosine

CAFFEINE & HEADACHES

Acute vs. Chronic Caffeine Exposure

- Chronic exposure can produce effects markedly different from acute exposures\(^1\)
- Chronic caffeine exposure
  - Up-regulation of adenosine receptors
  - Facilitates agonist binding to adenosine receptors
  - Marked tonic elevations in adenosine plasma concentrations\(^2\)\(^-\)\(^4\)
- This may reflect the differing actions of adenosine at different receptors/locations
  - Activation of A2A receptors on peripheral nerve terminals is pro-nociceptive, possibly through potentiation of the actions of CGRP
  - Activation of A1 receptors on these terminals is anti-nociceptive, possibly via inhibition of release of CGRP\(^5\)\(^,\)\(^6\)
  - An A2A receptor gene haplotype has been associated with migraine with aura\(^7\)

TREATMENT OVERVIEW:

- Sleep hygiene
- Rotate acute medications
- Taper off caffeine
- Hormonal preventive
  - Change Loestrin FE 1/20 to Lo-Loestrin FE 1/10 hs
MRM is associated with the late luteal phase decline in estrogen
Use of an OC that contains 20μg EE will not make the MRM better or worse.

The standard PFI of 7 days in very low dose pills often allows for ovulation to persist.
- Limiting the PFI to 2 days more reliably inhibits ovulation
- A 10μg EE decline is unlikely to trigger MRM
TREATMENT OVERVIEW:

- Sleep hygiene
- Rotate acute medications
- Taper off caffeine
- Hormonal preventive
- Migraine preventive
  - Consider triggers: menses, sleep, fasting, stress, weather
  - Atenolol 25mg q am
# Headache Calendars

**Baseline:** Ethinyl estradiol; norethindrone acetate FE 1/20

| S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S |
| xx | x | x | xx | x | xx | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x |

HA index = 51

**Post-treatment:** Ethinyl estradiol; norethindrone acetate FE 1/10

| S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S |
| xx | x | x | xx | x | xx | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x | xx | x |

0 severe, 0 moderate, 1 mild

HA index = 1
Meds:
Lo-Loestrin FE 1/10 hs
Atenolol 25 mg qd
Sumatriptan 100 mg 1/mon

Sleep History:
- Works straight days.
- Retires at 10:00 PM and falls asleep quickly.
- No nocturia.
- Arises at 6:15 AM feeling “refreshed.”

45 yr old neonatal NP with chronic migraine and MRM (now working straight days)
“Siri, I can’t sleep”

“I never said you could.”
**Effects of Hormones on Sleep**

**Estrogen:**
- Primarily affects REM sleep (↑)
- Weakens coupling of body temp/sleep–wake cycle
- Decreases SOL & WASO
- Increases TST

**Progesterone:**
- Primarily affects NREM
- Benzodiazepine–like
- Sedating effect
- Decreases SOL & WASO

Progestogens and Sleep

- Progestogens = progesterone &/or progestins
- Comparing CEE+MPA and CEE+Progesterone
  - Vasomotor symptoms improved in both groups
  - Subjective measures of sleep (questionnaires) improved in both groups
  - SE improved with progesterone but not with MPA
  - WASO also improved with progesterone but not with MPA

“Siri, what is peri-menopausal?”

“Peri is the Latin prefix meaning shut your flipping pie-hole.”
Menopausal Sleep Disturbances

- Total sleep time was comparable to controls
- Brief arousals averaged every 8 minutes
- 55 hot flashes/night (40 with arousals)
- Reduced slow-wave sleep
- 5-fold increased risk of sleep apnea without HRT; *no* increase with HRT

S. Woodward, 1997 North American Menopause Society Annual Meeting
True Hot Flashes

- 2–5 minutes in duration
- Mid-chest to head
- Steep onset—peak in 10–15 seconds
Non-hormonal Hot Surges

- Independent of menopausal status
- Physical/emotional triggers
- Gradual onset
Prevalence of Night Sweats in a Primary Care Practice

- 2267 adults, sampled during 1 week in the summer and 1 week in the winter
  - Ages 18–97 (mean 50.7 years)
  - 69% female
- <5% had complained of night sweats to their physicians
- 41% reported night sweats in past month
  - 23% with pure night sweats
  - 18% with night sweats and day sweats

Prevalence of Night Sweats in a Primary Care Practice

- Only variable associated with pure night sweats was panic attack
  - **WOMEN**: leading variables were hot flashes and panic attacks
  - **MEN**: leading variables were sleep problems, hot flashes (5%), and regular use of multivitamins
  - **ELDERLY**: only significant variable was sleep disorder

- Variables with night/day sweats: obesity, sleep problems, hot flashes, antihistamines, SSRIs, other (non-SSRI) antidepressants

Comfort Zone (~0.7° F)
Temperature Control & Sleep

Comfort Zone
“Siri, what is menstrual migraine?”

“Menstrual migraine is a disorder of the appendix.”
Thank You!

Anne H. Calhoun, MD, FAHS
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University of North Carolina, Chapel Hill