Brigham and Women's Hospital
Founding Member, Mass General Brigham

A case of chest pain, with a twist

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- Clinical focus: primary care
- Education and research focus: primary care career development

DISCLOSURES

I have no relevant disclosures.

OBJECTIVES

1. Engage in clinical reasoning to formulate a diagnostic and therapeutic plan for a patient presenting with chest pain.

[Four additional learning objectives to follow…]

Our Patient

37-year old woman
No chronic medical conditions
No prior hospitalizations or surgeries
No medications
G2P2

Works in healthcare, lives with husband and children, ages 5 and 2
No tobacco, minimal alcohol, walks 1.5 miles to and from work daily
FHx: HTN in both parents

Seen for routine physical January 2019, no concerns

July 2019: Urgent Care Visit for Chest Pain

Chest pain started on a Sunday evening
Had eaten a large BBQ meal earlier that day
The pain was left sided, pressure-like. Lasted 5 mins with self-resolution
There were no associated palpitations, nausea, dyspnea or diaphoresis
Did noticed “a dullness” in both arms during the episode
Not pleuritic; not worse or better with leaning forward or lying down
Not reproducible with palpation

Occurred 3 more times the following day, once possibly triggered by walking up stairs
Has not taken any medications for the symptoms, since they are transient
In office (Tuesday), completely **symptom-free**

July 2019: Urgent Care Visit for Chest Pain

BP 126/58, HR 68, SpO2 100%

Well-appearing

Pulmonary exam clear to auscultation throughout

Cardiac exam with regular rhythm, no murmur, no rub, no tenderness of chest wall, no edema, JVP <8

Abdomen non-tender throughout

Remainder normal

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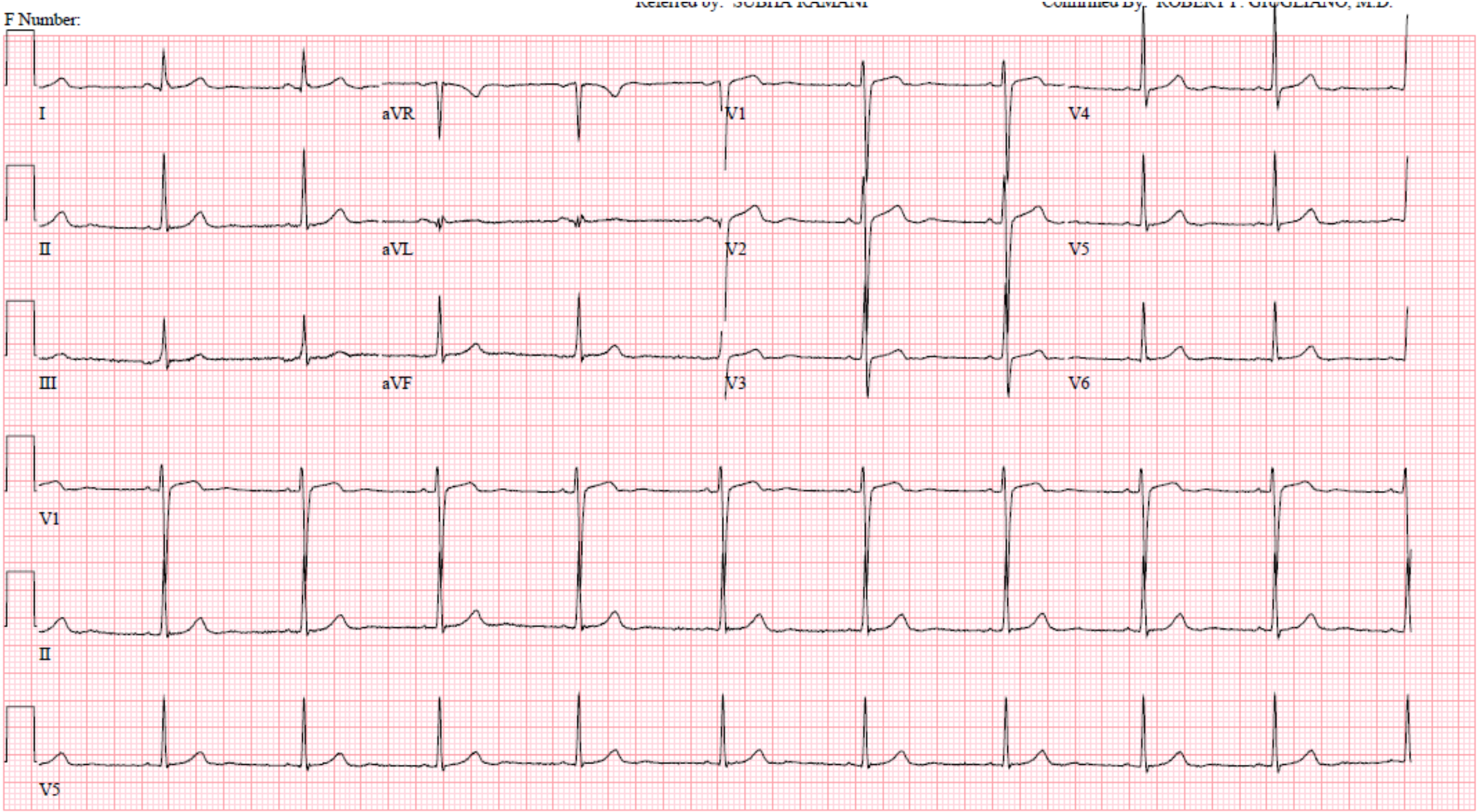


July 2019: Additional Results

Troponin <6

D-dimer 429 (nl <500)

Chest x-ray normal

Lipids 2016

- Total Chol 156
- HDL 55
- LDL 75
- TG 130

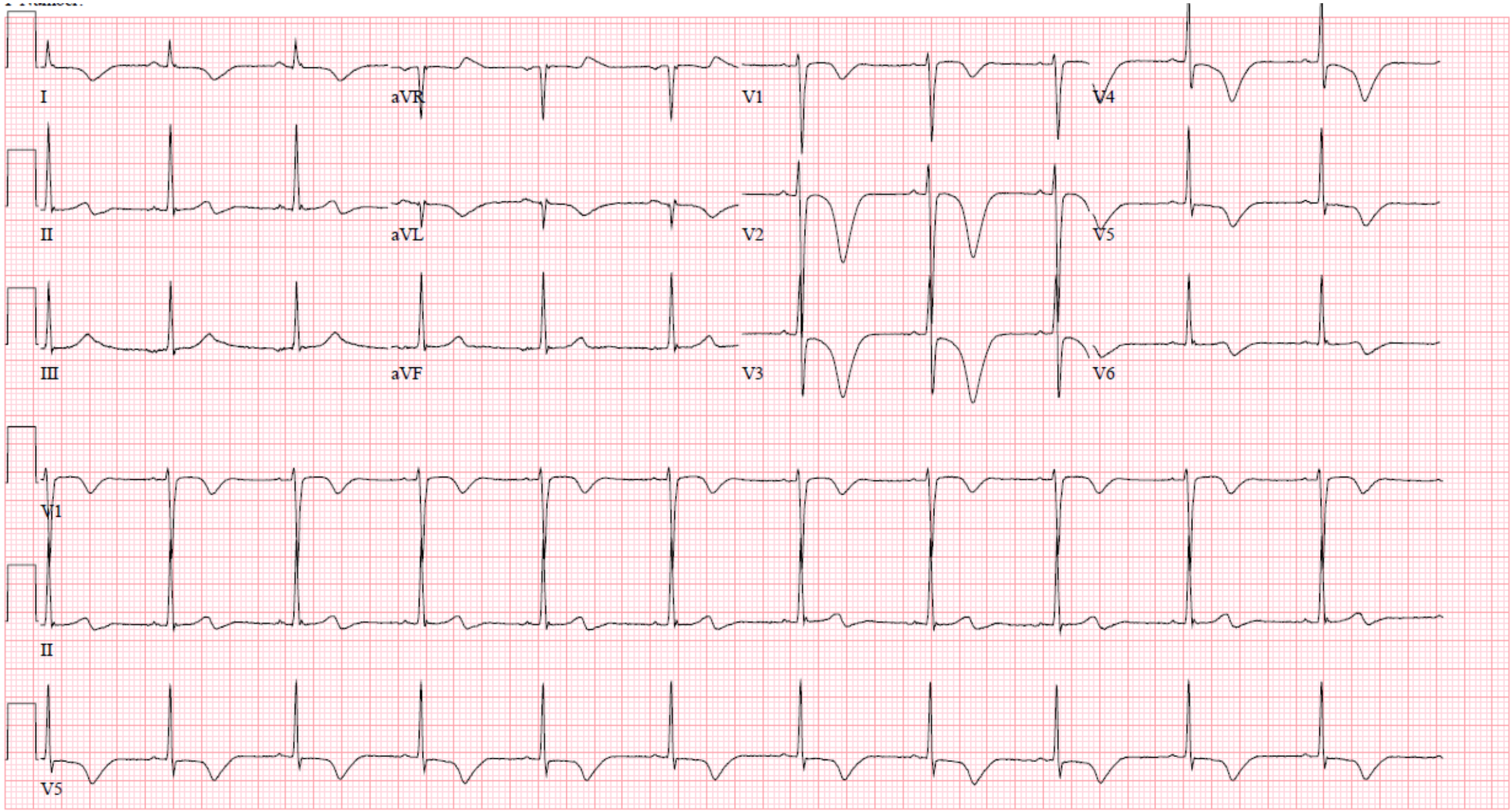
Next Steps?

A. Further diagnostics
B. Watchful waiting with return precautions

September 2019: Urgent Care Visit #2

Had had another episode mid-August, similar to July.
Now presents for evaluation on a Monday.
Chest pain recurred over the weekend, more severe, lasted up to 25 min. Occurred around 3-4 AM, waking from sleep.
Substernal, radiating to both arms. Newly assoc w/ diaphoresis.
Bending forward or being on hands and knees seems to help.
Famotidine and omeprazole did not seem to help.
Last episode was early in the morning on the day of clinic visit.
Chest pain free in clinic.

Exam with HR 68, BP 121/69
Cardiovascular exam unchanged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III
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V3
V6
V1
II
V5

Free Text:

What are your top 3 diagnostic possibilities?

September 2019: ED Visit

TnT 19, 19, 16 (normal <6)
D-dimer 301 (normal <500)
CXR unchanged

Remains chest pain-free
Given aspirin 325

Admitted to cardiology service
Heparin gtt and atorvastatin
Coronary cath planned for the next morning

Coronary Arteriography

Right dominant system.
Short left main with difficult engagement of the LAD.
The LAD is patent. No obstructive disease, dissection or embolism.
The LCX is widely patent. No abnormalities.
The RCA is patent.
The catheter dove in initially causing proximal vessel spasm which resolved with IC nitro. No abnormalities otherwise.

Cardiac MRI (done as outpatient) 9/2019

No myocardial perfusion defects.
No late gadolinium enhancement to suggest prior infarct, inflammation, or infiltration.
All chambers normal in size.

ESR 8
CRP 0.4
ANA negative

Diagnosed with Coronary Vasospasm

Started on Verapamil 240 mg and SL Nitro PRN

PCP visit after admission: bilateral soft femoral bruits – ultrasound without any arterial stenosis or wall abnormality.

March 2020 – ED visit for severe break-through episode while walking to work. Resolved with nitro. Verapamil up-titrated to 360 mg daily.

Overall doing well, occasional break-through episodes, always respond to nitro.

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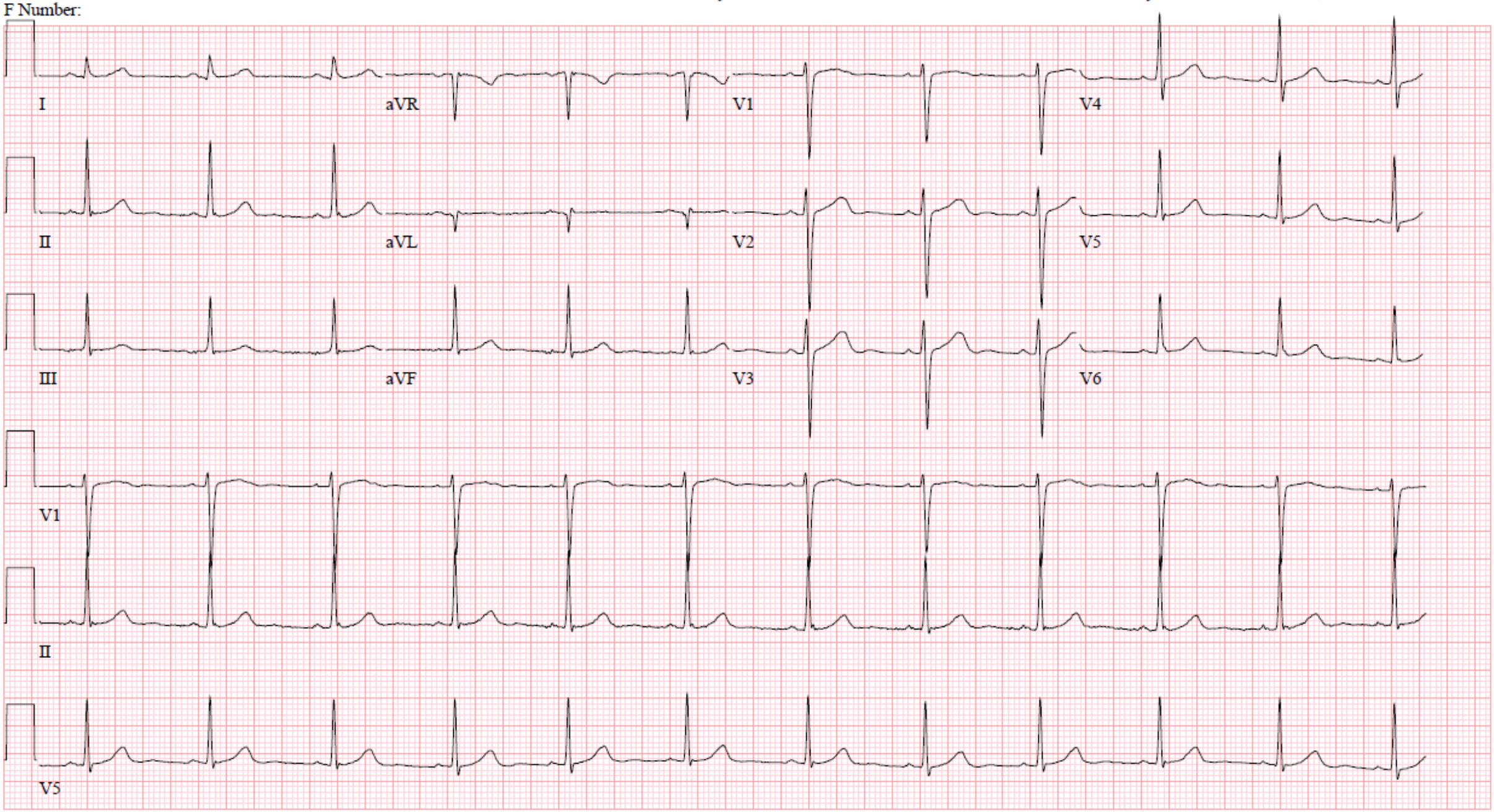
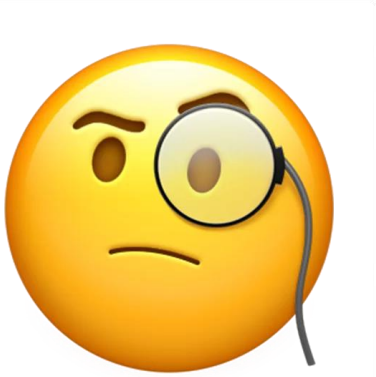


Routine Physical January 2021

“Doing well on Verapamil 360. However, does have some recrudescence if she misses a dose. She also notes that she has most of her break-through symptoms **in the 1-2 days prior to her menses** and that her original presentation also was immediately before menses.”



“Tell Me More...”

The July 2019 episode was the 1-2 days before her period.

The August 2019 episode was also the day before her period.

Verapamil dramatically helped.

Even on verapamil, can get a “build-up” prodrome in the days before period arrives. Not too bothersome – pressure more than pain.

Next Steps?

A. Continue current management with CCB and PRN nitro
B. Add standing doses of NTG, premenstrually
C. Start progestin-only contraceptive pills
D. Start combined estrogen/progestin contraceptive pills
E. I need to know the menstrual cycle for this case?!

Next Steps?

A. Continue current management with CCB and PRN nitro
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Case Follow-Up

Started combined OCPs in continuous fashion (skipping placebo pills)

Started with 20 mcg estrogen to make sure well-tolerated. Had break-through bleeding on this dose. Increased to 30 mcg estrogen dose.

Has not needed any nitro since she started OCPs.

Symptoms improved with initial OCP and improved even more with higher dose OCP.

OBJECTIVES, Revisited

1. Engage in clinical reasoning to formulate a diagnostic and therapeutic plan for a patient presenting with chest pain.
2. Recognize and appropriately treat vasospastic angina.
3. Describe the hormonal pattern of the menstrual cycle.
4. Recognize implications of the menstrual cycle for the diseases we treat as internists.
5. Describe various approaches to the treatment of catamenial phenomena to optimize outcomes and quality of life.

Vasospastic Angina

Prevalence difficult to estimate – not all cases come to attention
May be present in up to 40% of patients with suspected coronary disease and no epicardial obstructive lesions

Prevalence may be higher in males

Cigarette smoking is a risk factor
Cocaine use is also a risk factor

J Am Heart Assoc. 2022;11(7)

Vasospastic Angina – Diagnostic Criteria

(1) **Nitrate-responsive angina** — during spontaneous episode, with at least one of the following:

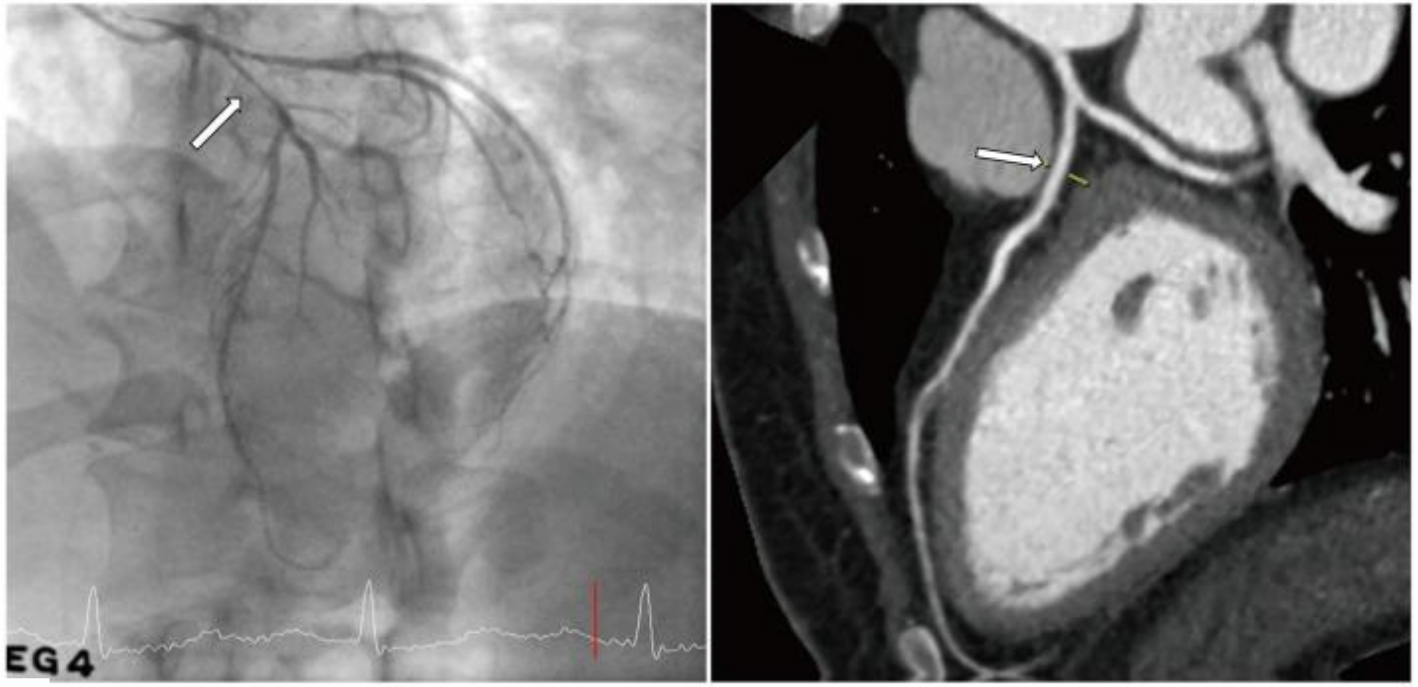
(a) Rest angina—especially between night and early morning
(b) Diurnal variation in exercise tolerance—reduced in morning
(c) Hyperventilation can precipitate an episode
(d) Calcium channel blockers (but not β-blockers) suppress episodes

(2) **Transient ischemic ECG charges** during spontaneous episode

(3) **Angiographic evidence of coronary artery spasm**

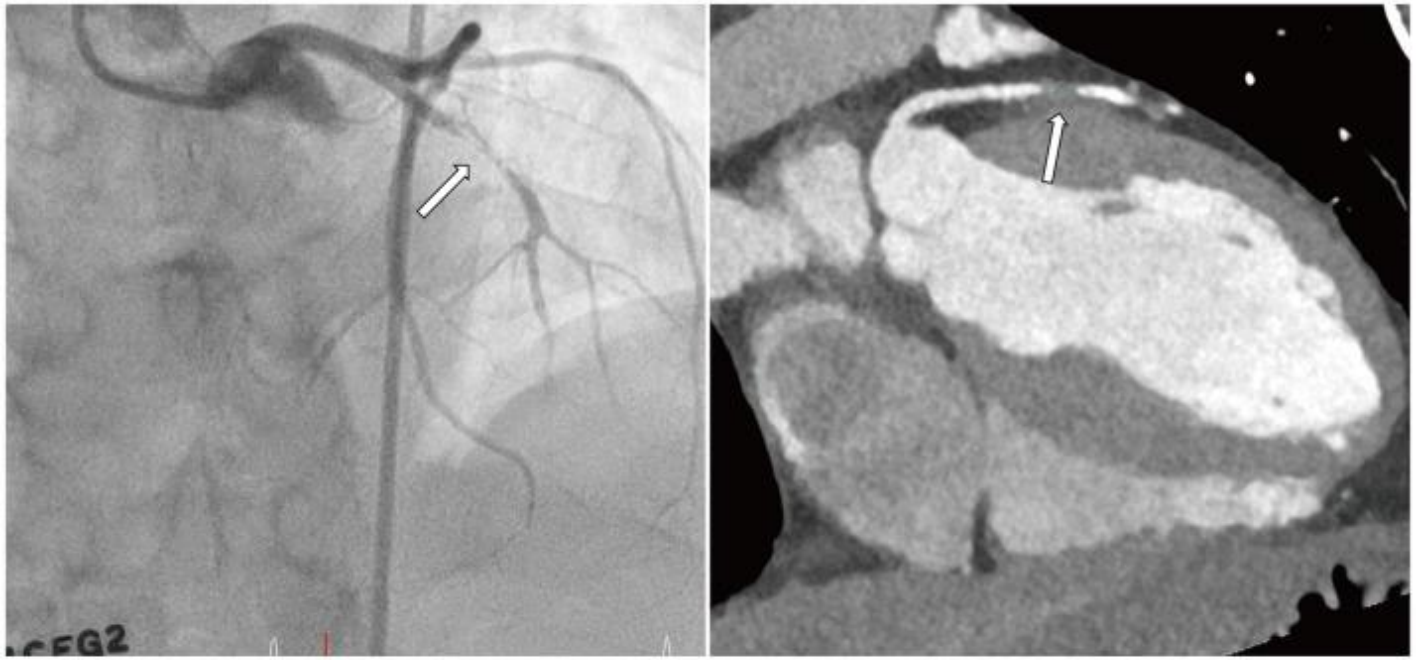
Definite vasospastic angina = 1 and 2 *or* 3
Suspected vasospastic angina = 1 with equivocal 2 or 3

COVADIS – Coronary Vasomotor International Study Group 2015



Invasive angiography

coronary CTA



Slide courtesy of Dr. Marie Gerhard Herman

Vasospastic Angina – Diagnosis

Classic symptoms and transient EKG changes with low ASCVD risk
→ **Can treat for vasospasm empirically**

Clinically suspected vasospasm with intermediate to high ASCVD risk

→ **Requires stress testing, CCTA or coronary arteriography to exclude atherosclerotic coronary disease**

CLINICAL VASOSPASM

Slide courtesy of Dr. Marie Gerhard Herman

All Vasospastic Conditions Share Pathophysiology

Triggering Stimuli

- High adrenergic tone
- Inflammation
- Oxidative stress
- Shifting estrogen or androgen

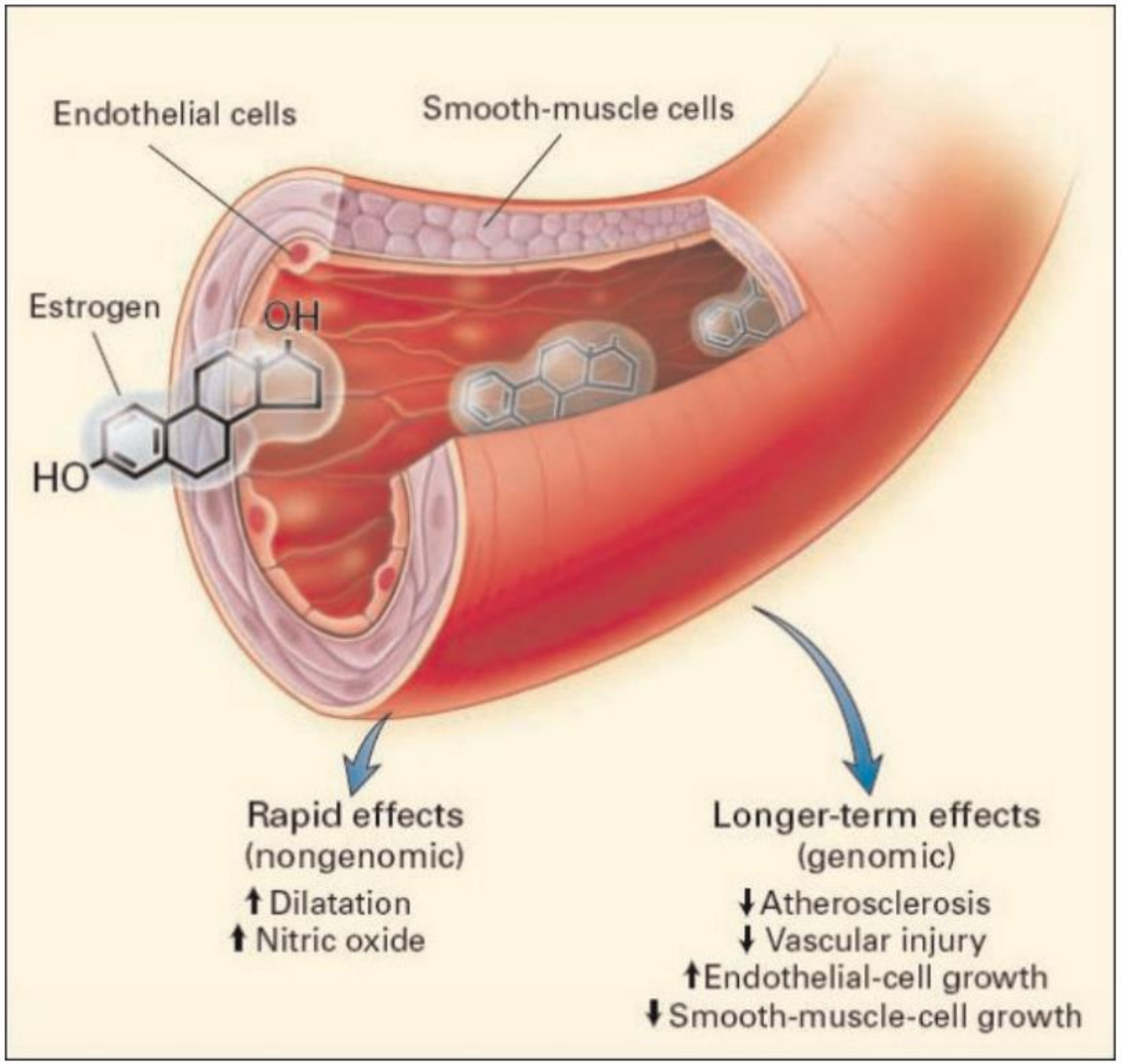
Vascular Abnormalities

- Smooth muscle hypercontractility
- Endothelial function abnormality
- Atherosclerosis, arteritis, vascular injury

Genetic Factors

Slide adapted from Dr. Marie Gerhard Herman

The Effects of **Estrogen** on Vascular Function



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Dr. Marie Gerhard
Herman

Therapy for Coronary Vasospasm

Pillars:

Lifestyle - smoking cessation, exercise

Calcium channel blockers - verapamil, diltiazem

Short-acting nitrates PRN

Possibilities:

Long-acting nitrates?

Magnesium? (IV vasodilates, oral data are limited)

Implantable defibrillator (considered for those with VT, VF presentation)

OBJECTIVES, Revisited

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3. Describe the hormonal pattern of the menstrual cycle.
4. Recognize implications of the menstrual cycle for the diseases we treat as internists.
5. Describe various approaches to the treatment of catamenial phenomena to optimize outcomes and quality of life.

Are symptoms definitively associated with the menstrual cycle?

May seem to patient to be monthly but actually not associated with menstrual cycle, eg "*I always get symptoms on the first day of each month*"

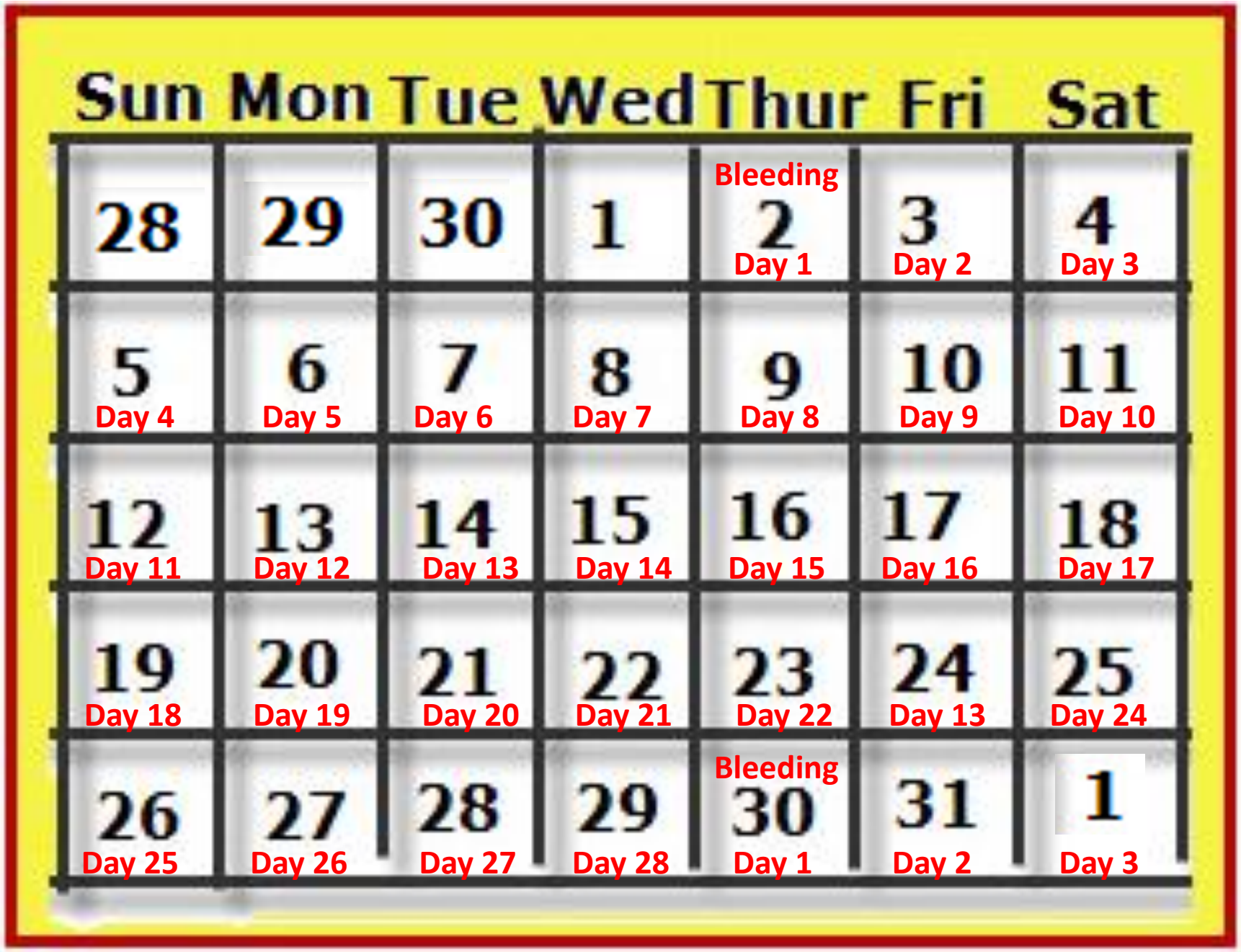
Have patient log daily symptoms with day of the menstrual cycle

First day of menstrual bleeding = Day 1

Most women don't have 30-day cycles (21-35 days)

Slide courtesy of
Dr. Ellen Seely

Menstrual Diary: the old-fashioned way



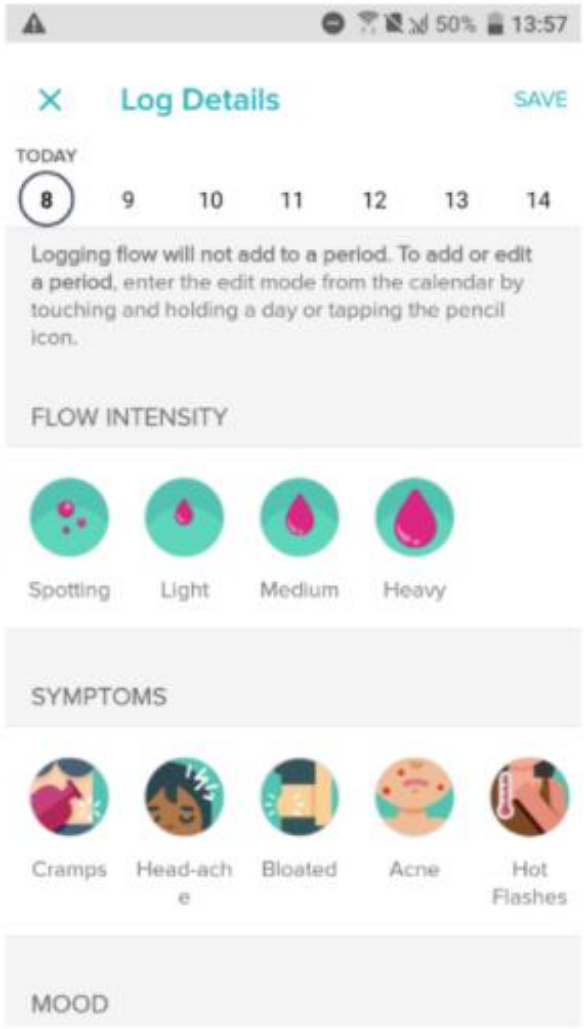
Sun	Mon	Tue	Wed	Thur	Fri	Sat
28	29	30	1	Bleeding 2 Day 1	3 Day 2	4 Day 3
5 Day 4	6 Day 5	7 Day 6	8 Day 7	9 Day 8	10 Day 9	11 Day 10
12 Day 11	13 Day 12	14 Day 13	15 Day 14	16 Day 15	17 Day 16	18 Day 17
19 Day 18	20 Day 19	21 Day 20	22 Day 21	23 Day 22	24 Day 13	25 Day 24
26 Day 25	27 Day 26	28 Day 27	29 Day 28	Bleeding 30 Day 1	31 Day 2	1 Day 3

Slide courtesy of Dr. Ellen Seely

Menstrual Diary: the old-fashioned way

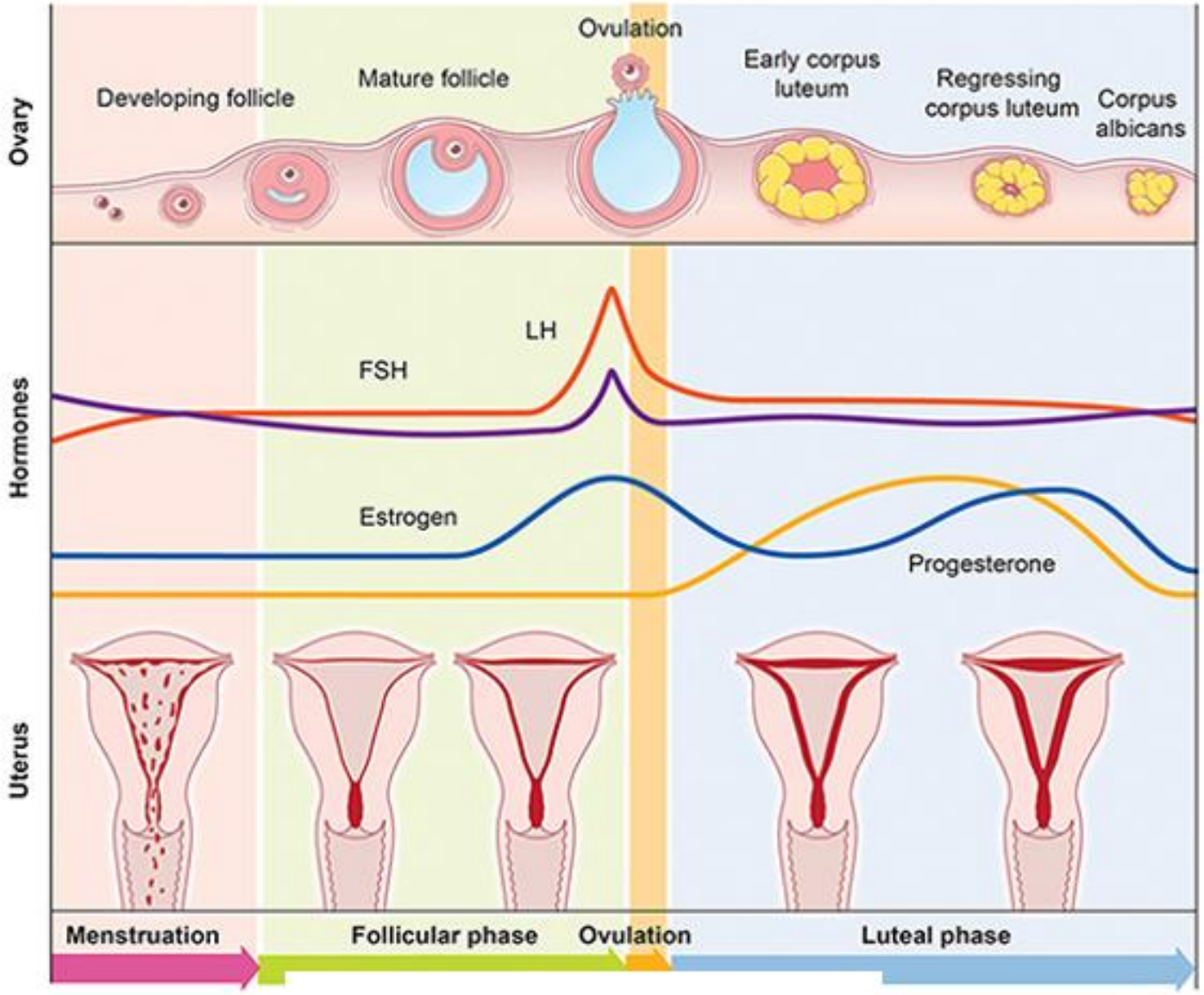
Slide courtesy of
Dr. Ellen Seely

Tracking with a Digital Tool

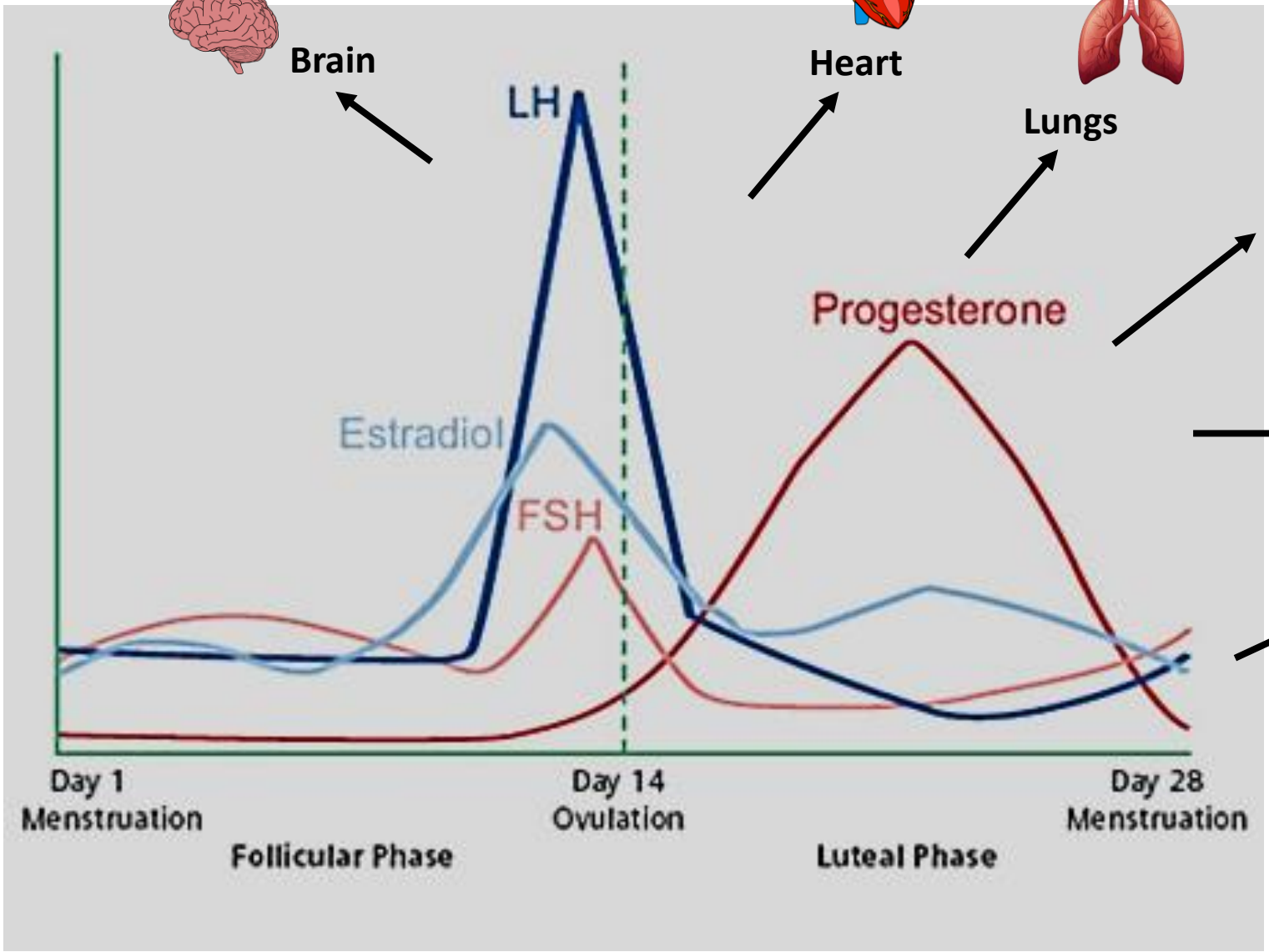


On Fitbit©

An Obstetrics and Gynecology View of the Menstrual Cycle



An Internist's View of the Menstrual Cycle



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Dr. Ellen Seely

Examples of menstrual cycle exacerbated medical conditions

- Psychiatry: premenstrual dysphoric disorder (PMDD)
- Neurology: menstrual migraines, catamenial epilepsy
- Dermatology: premenstrual acne
- Rheumatology: rheumatoid arthritis
- Gastroenterology: irritable bowel syndrome
- Pulmonary: perimenstrual asthma
- Endocrinology: diabetes (luteal phase increase in insulin requirement)
- Cardiology: vasospastic angina

Menstrual Cyclic Variation of Myocardial Ischemia in Premenopausal Women with Variant Angina

Hiroaki Kav
Hisao Oga

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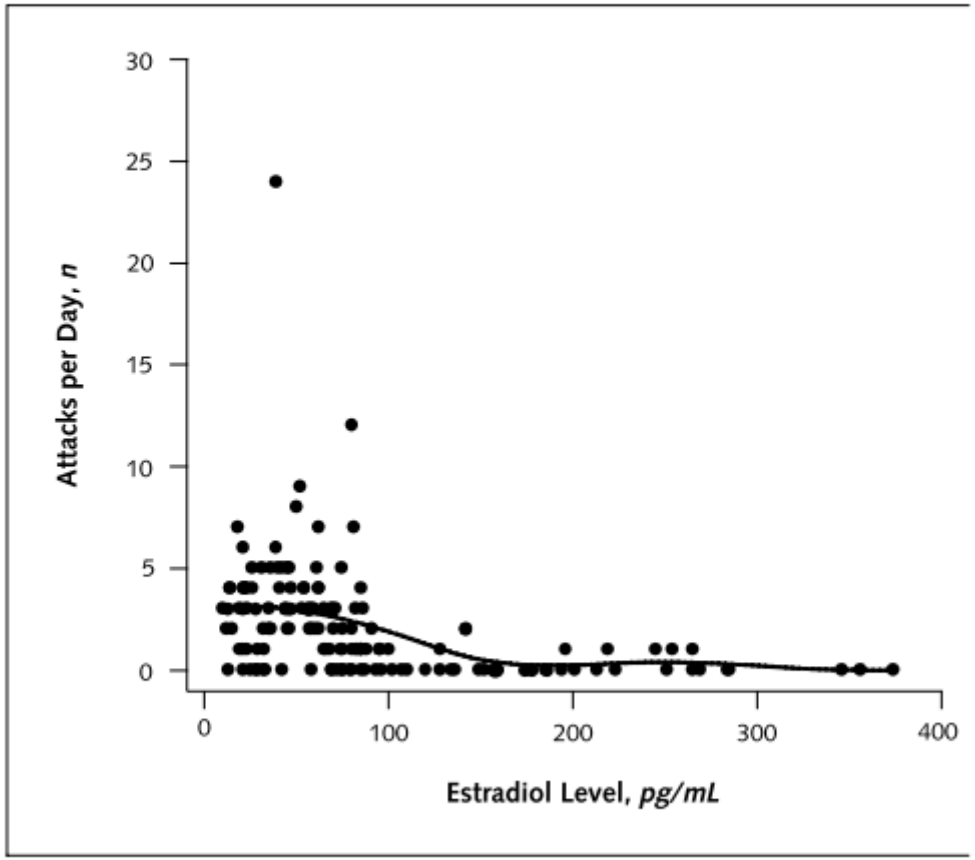
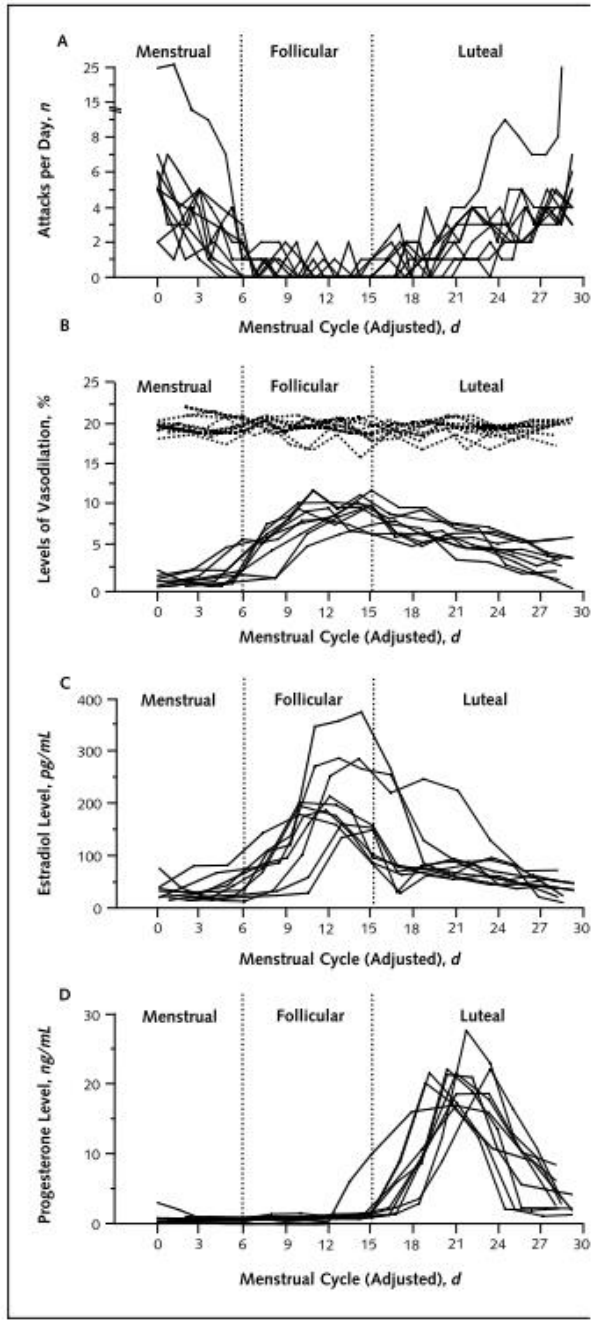
Figure 2. **Scatterplots and smooth curves of serum estradiol levels versus myocardial ischemic episodes.**



Smooth curves were fit by using kernel estimation.

Figure 1. **Myocardial ischemic episodes and levels of vasodilation, estradiol, and progesterone in study participants, according to menstrual-cycle phase.**



Treating catamenial exacerbations of medical conditions – **two pathways**

First, are symptoms really linked to menstrual cycle?
If so, which phase of the cycle and what is happening then hormonally?

Pathway 1: Intensify monitoring or treatment regimen for the underlying condition at specific time of cycle (e.g. diabetes, asthma, migraine)

Pathway 2: Ablation of hormonal cycling

- Combined oral contraceptives – continuous fashion
- Estradiol patch and oral micronized progesterone – continuous
- GNRH agonist (Lupron) +/- add back E/P

Questions and Discussion

MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

Vasospastic angina presents with spontaneous episodes of chest pain of ischemic nature. Episodes classically occur at rest, in early morning hours, may be precipitated by hyperventilation and are highly responsive to nitrates.

Definitive diagnosis requires symptoms + either EKG changes or visualized coronary vasospasm. If ASCVD risk intermediate to high, stress testing, CCTA, or angiography required to exclude atherosclerosis.

The pathophysiology of coronary vasospasm overlaps with other vasospastic conditions, and these can co-occur in the same individual.

Estrogen is a vasodilator and a fall in estrogen can precipitate vasospastic episodes.

Numerous medical conditions managed by the internist can fluctuate with the menstrual cycle. To diagnose catamenial phenomena, carefully track the symptoms over the course of multiple menstrual cycles. Treatment of catamenial phenomena can involve cyclical treatment intensification or pharmacologic stabilization of hormone fluctuation.

Acknowledgments

Our Patient
Dr. Ellen Seely, Division of Endocrinology, BWH
Dr. Marie Gerhard-Herman, Division of Cardiology, BWH

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