PREMENSTRUAL DISORDERS

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LARC
Mentoring Program

DISCLOSURES

Jen Robinson, MS, WHNP-BC, CNM (*she, her*) has the following

Financial relationships to disclose: Merck Nexplanon trainer

Non financial relationships: working mom, loves baby animals

UNM LARC MENTO
PROGRAM

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OBJECTIVES

1. Define premenstrual syndrome and premenstrual dysphoric disorder
2. Review hormonal contraceptive treatments for premenstrual disorders
3. Review non-hormonal treatments for premenstrual disorders
4. **Share photos of baby animals**

Photo credit:
https://www.pinterest.com/pin/6874169278 9/

SHARED CRITERIA – PMS AND PMDD

* Symptom expression during luteal phase
* With symptom free period (of time)
* Functional impairment associated with condition

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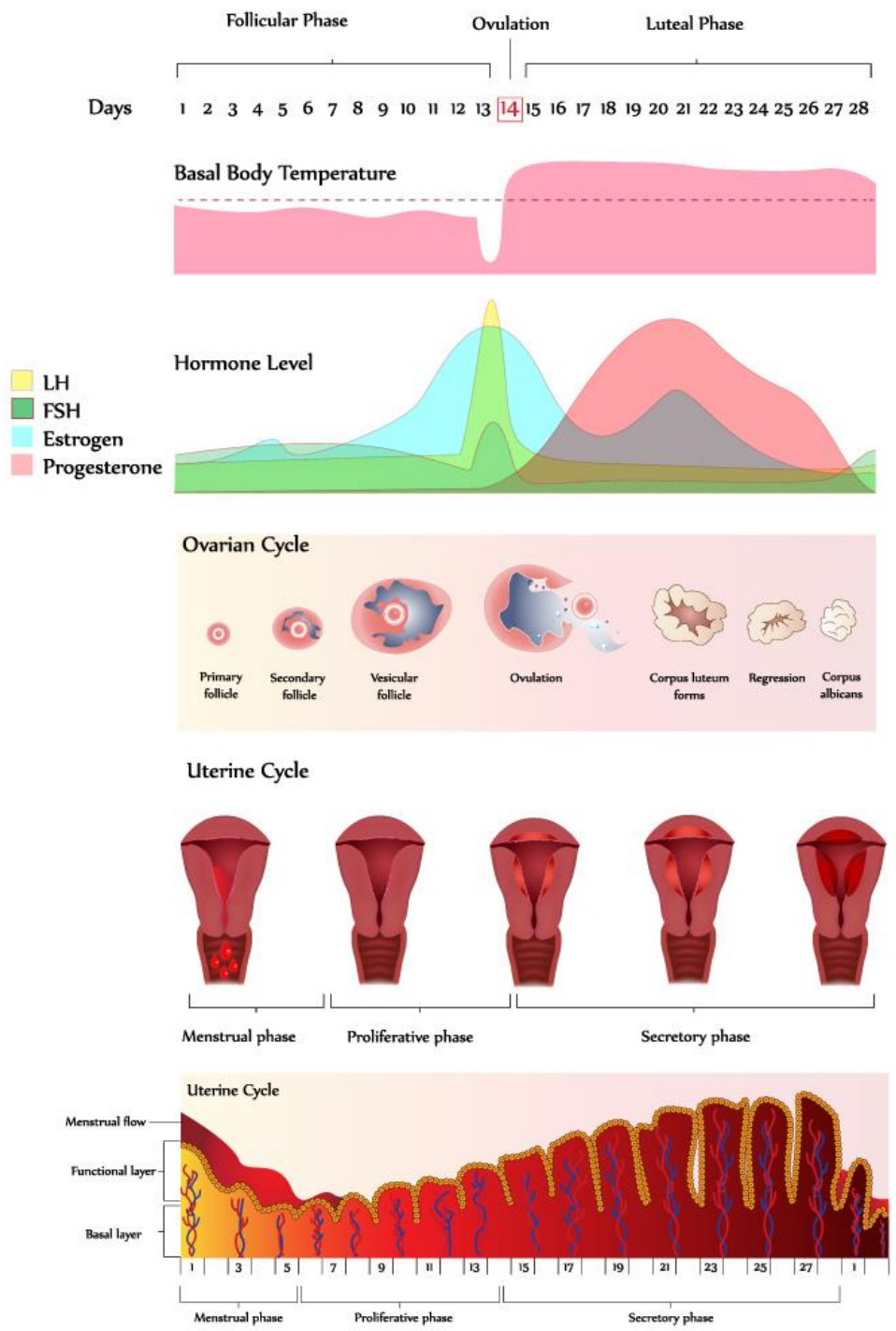
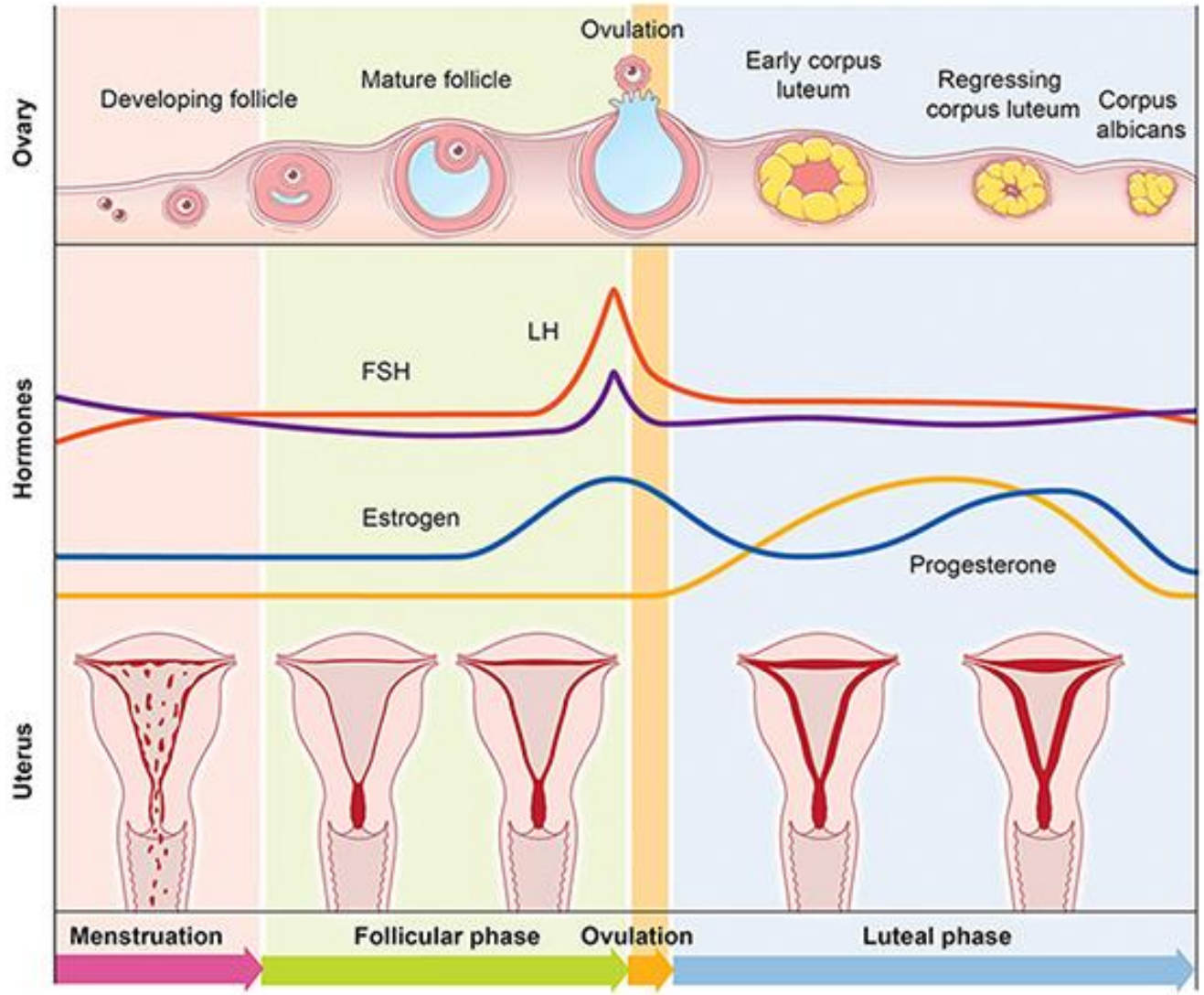
Image credit: https://www.rainbowfertility.com.au/family-building-for-lesbians/female-




Ovary
Developing follicle
Mature follicle
Ovulation
Early corpus luteum
Regressing corpus luteum
Corpus albicans
Hormones
LH
FSH
Estrogen
Progesterone
Uterus
Menstruation
Follicular phase
Ovulation
Luteal phase

babycenter

DEFINITION: PREMENSTRUAL SYNDROME

TABLE 2
Premenstrual syndrome[3]

1) Physical and or emotional symptoms
2) Symptoms are present during luteal phase and abate as menstruation begins
3) A symptom-free week
4) Symptoms are associated with significant impairment during luteal phase

Yonkers. Premenstrual disorders. Am J Obstet Gynecol 2018.

If physical manifestations cause functional impairment →

Diagnosis of PMS can be made in absence of severe emotional symptoms

DEFINITION: PREMENSTRUAL DYSPHORIC DISORDER

TABLE 1

***Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[4] premenstrual dysphoric disorder**

A. In most menstrual cycles, following symptoms must be present in final week before onset of menses, start to *improve* within few days after onset of menses, and become *minimal or* absent in week postmenses—at least 1 symptom must be either (1), (2), (3), or (4) and individual must experience at least 5 total symptoms:
   1. Marked affective lability (eg, mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection)
   2. Marked irritability or anger or increased interpersonal conflicts
   3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts
   4. Marked anxiety, tension, feelings of being "keyed up," or "on edge"
   5. Decreased interest in usual activities (eg, work, school, friends, hobbies)
   6. Subjective difficulty in concentration
   7. Lethargy, easy fatigability, or marked lack of energy
   8. Marked change in appetite, overeating, or specific food cravings
   9. Hypersomnia or insomnia
   10. A sense of being overwhelmed or out of control
   11. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, sensation of "bloating," weight gain

B. Symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships

C. Disturbance is not merely exacerbation of symptoms of another disorder

D. Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles (diagnosis may be made provisionally prior to this confirmation)

E. Symptoms are not due to direct physiological effects of substance (eg, drug of abuse, medication or other treatment) or another medical condition (eg, hyperthyroidism)

Yonkers. Premenstrual disorders. Am J Obstet Gynecol 2018.

Photo credit:https://www.pinterest.com/pin/208995857

PREMENSTRUAL SYMPTOM DETAILS

- Somatic symptoms – most common
  - Breast pain, bloating, swelling, headache
- Affective symptoms – most common
  - Depression, irritability, anxiety, fear of rejection
- Core feature:
  - recurrent onset of symptoms during the end of the luteal phase of the menstrual cycle
  - with a symptom-free period shortly after menses has begun, typically when the menstrual flow has ended
  - symptoms most severe the day before and first day of menses

AJOG 2018
Up to date 2020

NOT ALL BAD?

“PMS makes me feel more connected to myself, bolder and braver. I made some important life decisions during times of PMS!” -Tamires

“A deeper understanding of who I am. An urge to be alone. A sense of peace. Physical acceptance. Ability to let go.” -Chelsea

Chrisler et al. Self-Silencing, Perfectionism, Dualistic Discourse, Loss of Control, and the Experience of Premenstrual Syndrome. Women’s Reproductive Health. 2014 Jul 3;1(2):138-52.

Image credit: https://helloclue.com/

PROVIDERS LESS LIKELY TO BELIEVE TRANS, NON-BINARY, BLACK, & LATINA PATIENTS

Trans and non-binary individuals report many experiences with provider disbelief, false assumptions, and inability to look beyond their identity when they reported physical and emotional premenstrual symptoms (Moseson 2020)

African American and Latina women identify the normalization/dismissal of pain, symptoms, and experiences, and feelings of not being taken seriously by medical providers (Martinez 2020)

Moseson et al. The Imperative for Transgender and Gender Nonbinary Inclusion, Obstetrics & Gynecology: May 2020
Martinez, L. (2020). Racial Injustices: The Menstrual Health Experiences of African American and Latina Women.

APPROACH TO EVALUATION

- Laboratory testing not useful. Daily serum concentrations of gonadotropins and sex steroids are no different in people with or without PMS
- Prospective daily symptom recording for two months → determine if symptoms present continuously or during premenstrual phase
- Rule out chronic mood disorder
- Consider endocrine disorders that can cause similar symptoms (thyroid disease, cortisol excess)

AJOG 2018
Up to date 2020

DAILY RECORD OF SEVERITY OF PROBLEMS

6 point scale

11 symptoms/problems

Record of timing of spotting/bleeding

3 indicators of functional impairment

- home, work, school
- participation in hobbies
- relationships

Daily record of severity of problems

Please print and use as many sheets as you need for at least two FULL months of ratings.

Name or initials: Month/year:

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity:
1 - not at all, 2 - minimal, 3 - mild, 4 - moderate, 5 - severe, 6 - extreme.

Enter day (Monday = "M", Thursday = "R", etc) >
Note spotting by entering "S" >
Note menses by entering "M" >
Begin rating on correct calendar day > 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

1. Felt depressed, sad, "down", or "blue", or felt hopeless, or felt worthless or guilty
2. Had loss of interest, "keyed up", or "on edge"
3. Had mood swings (ie, suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt
4. Felt angry, or irritable
5. Had less interest in usual activities (work, school, friends, hobbies)
6. Had difficulty concentrating
7. Felt lethargic, tired, or fatigued; or had lack of energy
8. Had increased appetite or overate; or had cravings for specific foods
9. Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep
10. Felt overwhelmed or unable to cope; or felt out of control
11. Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms
- At work, school, home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency
- At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities
- At least one of the problems noted above interfered with relationships with others

EPIDEMIOLOGY

Retrospective reports of symptom timing vary, but show PMS & PMDD across the world

PMS: 20-30% of menstruating people

PMDD: 1.2-6.4%

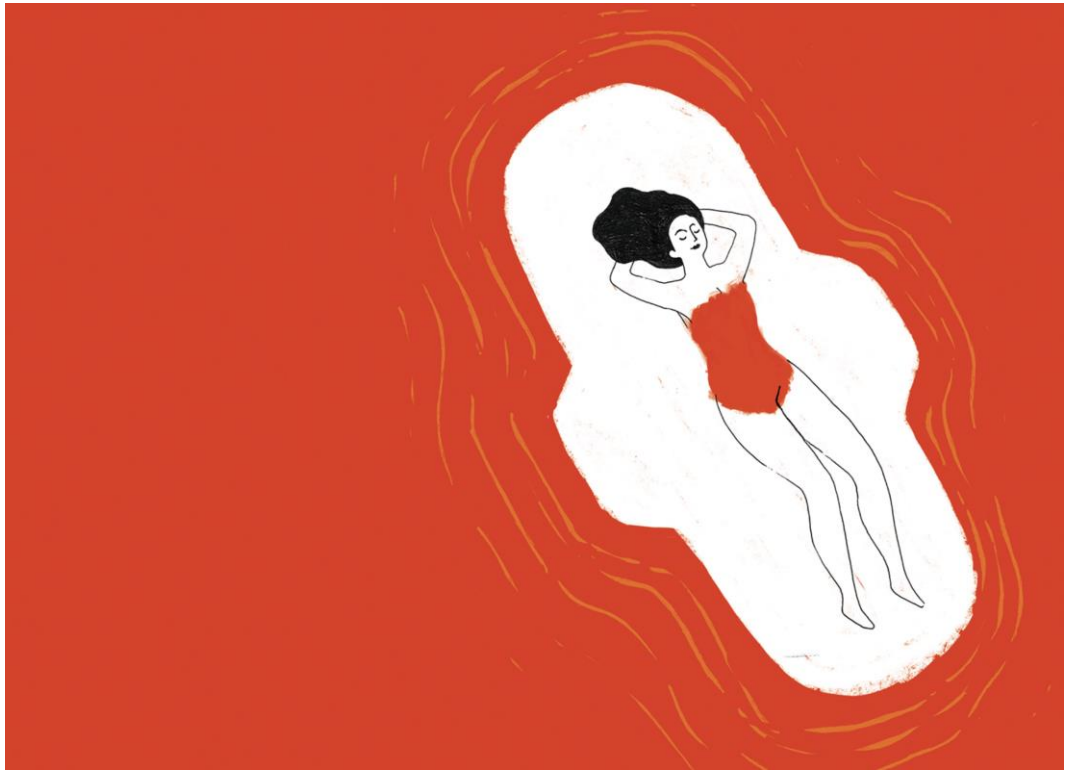


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Image credit:
https://steemit.com/health

RISK FACTORS

- No difference in age groups
- More prevalent in white vs black people
- BMI >27.5
- Metabolic syndrome
- Cigarette smoking
- Early sexual abuse/trauma
- Comorbidity with anxiety and depressive disorders

Photo credit: https://www.pinterest.com/vegnews/adorable-baby-animals/

DIETARY FACTORS

Protective, high intake of:

Thiamine
Riboflavin
Non-heme iron

Might increase risk:

High potassium intake

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Image credit: https://www.nyas.org/media/22430/2019-thiamine-workshop-1-report.pdf

ETIOPATHOLOGY – THEORY #1

"Pathological" response to withdrawal from or exposure to progesterone metabolite allopregnanolone

→ some SRIs impact allopregnanalone

→ tx eliminating cyclic changes in ovarian hormones would help

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ETIOPATHOLOGY – THEORY #2

Serotonin transporter dysregulated

Sex steroids and their receptors
- abundant in brain regions that
- regulate emotion and behavior
- & they modulate serotonin transmission

→ "treatments that stabilize emotional symptoms and impulsivity can be beneficial"

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EVIDENCE BASED TREATMENTS

- Nonpharmacological
- Serotonin reuptake inhibitors
- Hormone agonists and antagonists
- Surgery
- Complementary medicines

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Image credit:
https://www.pinterest.com/pin/73184

NONPHARMACOLOGICAL APPROACHES

Complex carbohydrate intake during luteal phase → increases serotonin available centrally

Cognitive behavioral therapy (as effective as fluoxetine)

Exercise?!

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Image credit: https://www.diabetes.org/nutrition/understanding-carbs

SEROTONIN REUPTAKE INHIBITORS

Throughout menstrual cycle

Fewer tolerability issues than intermittent dosing

Fewer transient adverse effects – N/V/GI/H

Less withdrawal – flu like symptoms, anxiety, jitteriness, “brain zaps”

During luteal phase

Rapid onset of action for PMDD (& those on threshold)

Some evidence shows greater improvement vs continuous dosing (some does not :/)

Therapeutic doses often require titration for tolerability of transient adverse effects

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Personal email communication, Amre A Elmaoued, PharmD, clinical psychiatry faculty member at UNM College of Pharmacy, 10/26/20

ANTIDEPRESSANT MEDICATION

- SSRI – most studied for PMDD
  - Sertraline, fluoxetine, paroxetine, citalopram
  - Improvement in PMDD sx compared to placebo

- TCAs – primarily clomipramine
- SNRI – venlafaxine

- If withdrawal symptoms with luteal phase dosing…
  - SSRI with long half life to prevent withdrawal syndrome (fluoxetine)
  - Avoid shorter half lives (paroxetine, SNRIs like venlafaxine)

Ayoc 2018,
Personal email communication, Amre A Elmaoued, PharmD, clinical psychiatry faculty member at UNM College of Pharmacy, 10/26/20

Premenstrual dysphoric disorder (PMDD): Suggested daily dosing for continuous and intermittent regimens

SSRI	Starting dose (half suggested effective dose)	Usual effective doses	Maximum after several cycles if further titration is needed for symptom control
Citalopram	10 mg	20 to 30 mg	Continuous: 40 mg Intermittent: 30 mg
Escitalopram	5 to 10 mg	10 to 20 mg	Continuous: 20 mg Intermittent: 20 mg
Fluoxetine	10 mg	20 mg	Continuous: 30 mg Luteal phase: 30 mg Symptom onset: 20 mg
Paroxetine (IR)	10 mg	20 to 30 mg	Continuous: 40 mg Intermittent: 30 mg
Sertraline	25 mg	50 to 150 mg	Continuous: 200 mg Intermittent: 150 mg

Suggestions for dose titration using citalopram as an example:

- Starting dose is 10 mg; increase in 10 mg increments as tolerated.
- For symptom-onset dosing: Initial: 10 mg once daily from the day of symptom onset until a few days after the start of menses; may further increase dose based on response and tolerability (eg, in 10 mg increments) per menstrual cycle up to a maximum of 30 mg/day.[1]
- For intermittent regimens (luteal phase or symptom-onset): After approximately 6 months, many women are able to accommodate to a higher starting dose (ie, they can initiate each cycle with the ultimate therapeutic dose [20 to 30 mg] rather than the initial 10 mg dose).

SSRI: selective serotonin reuptake inhibitor; IR: immediate release.

Reference:

1. *Ravindran LN, Woods SA, Steiner M, Ravindran AV. Symptom-onset dosing with citalopram in the treatment of premenstrual dysphoric disorder (PMDD): a case series. Arch Womens Ment Health 2007; 10:125.*

Courtesy of Kimberly Yonkers, MD.

HORMONE AGONISTS AND ANTAGONISTS

- Combination OCPs – cyclic
  - ethinyl estradiol 20 mcg/**drospirenone** 3 mg (**24 active tabs**) and 4 placebo tabs per pack
  - Yaz, Gianvi, Loryna, & Beyaz confirmed. Unsure – Nikki, Lo-Zumandimine, Melamisa

- Combination OCPs – continuous
  - Daily levonorgestrel 90 mcg/ethinyl estradiol 20 mcg – evidence support variable

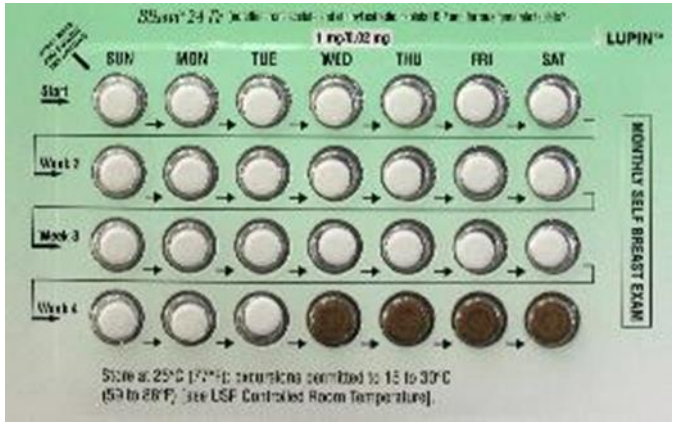

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Image credit: Hatcher et al, 2018

HORMONE AGONISTS AND ANTAGONISTS

- Gonadotropin-releasing hormones (GnRH) agonists
  - Third line agent behind SSRI and oral contraception
  - Suppress ovarian release of estrogen & ovulation
  - Leuprolide acetate 3.75 mg IM monthly
  - Hypoestrogenic state → vaginitis, vasomotor sx, decrease bone density
  - Expensive

- Estrogen (oral, patch, implant) or progestin
  - Data in support – from poor quality research
  - Can provoke symptoms

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Photo credit: Round boys, instagram

SURGERY – FOR REFRACTORY SYMPTOMS

Total hysterectomy with bilateral salpingo-oophorectomy

Before surgery, try GnRH agonist to
--produce similar effect
--assess benefit & tolerance of hypoestrogenic state

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Image credit: reddit

COMPLEMENTARY MEDICINES

- Vitamin B6 – most studied
  - Cochrane review – up to 100 mg/d
- Calcium 500 mg
  - Influences neuromodulation, low calcium in pt with PMS

- Vitex (chasteberry) 20-40 mg/d
  - Binds to dopamine, opioid, beta estrogen receptors
- St John wort
  - *caution in combo with OCPs, SSRIs*
  - Bloating, food cravings, headache, fatigue improved
  - No improvement with mood or pain
- Gingko biloba
  - Luteal phase through menses start, TID
  - Anti-inflammatory – decrease stress, depressive sx, physical sx w/in one month

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Image credit:
https://tucsoncleanandbeautiful.org/produ

APPROACH TO MANAGEMENT

1. Symptoms began in premenstrual phase, offset at beginning of menses (PMS, PMDD)
2. Ongoing symptoms that worsen during the premenstrual phase (premenstrual worsening of another condition)
3. Continuous or sporadic symptoms not related to phase of menstrual cycle (neither PMS nor PMDD)

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MGMT - PREMENSTRUAL SYMPTOMS LIMITED TO PREMENSTRUAL PHASE (PMS, PMDD)

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First line per RCOG

Exercise

Vit B6 100 mg

CBT

OCPs (24/4 with drospirenone)

Intermittent or continuous SSRIs

If mild sx or don't want rx

Complex carb during luteal phase

Exercise

Vit B6 100 mg daily

Calcium 1000 mg daily

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MGMT - PREMENSTRUAL SYMPTOMS LIMITED TO PREMENSTRUAL PHASE (PMS, PMDD)

- When to consider SSRI…
  - Moderate to severe PMS and do not need contraception
  - Drospirenone/estradiol OCPs not effective
  - Contraindication to or prefer to avoid estrogen

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Image credit: https://www.psychiatryadvisor.com/home/topics/mood-disorders/new-analysis-reconfirms-effectiveness-of-ssri-antidepressants/

MGMT – ONGOING SYMPTOMS THAT WORSEN IN THE PREMENSTRUUM

1. Evaluate and treat underlying disorder
2. If depression or anxiety is underlying disorder, consider:
   - Daily continuous SRI
   - Exercise and nutrition recommendations
   - Vit B6 100 mg/day
   - Calcium 1000 mg/day
3. If above not sufficient, consider:
   - Increase dose of SRI during luteal phase
   - Add drospirenone/estradiol 24/4 OCP
   - GnRH agonists will not substantially help people with depressive symptoms during follicular phase

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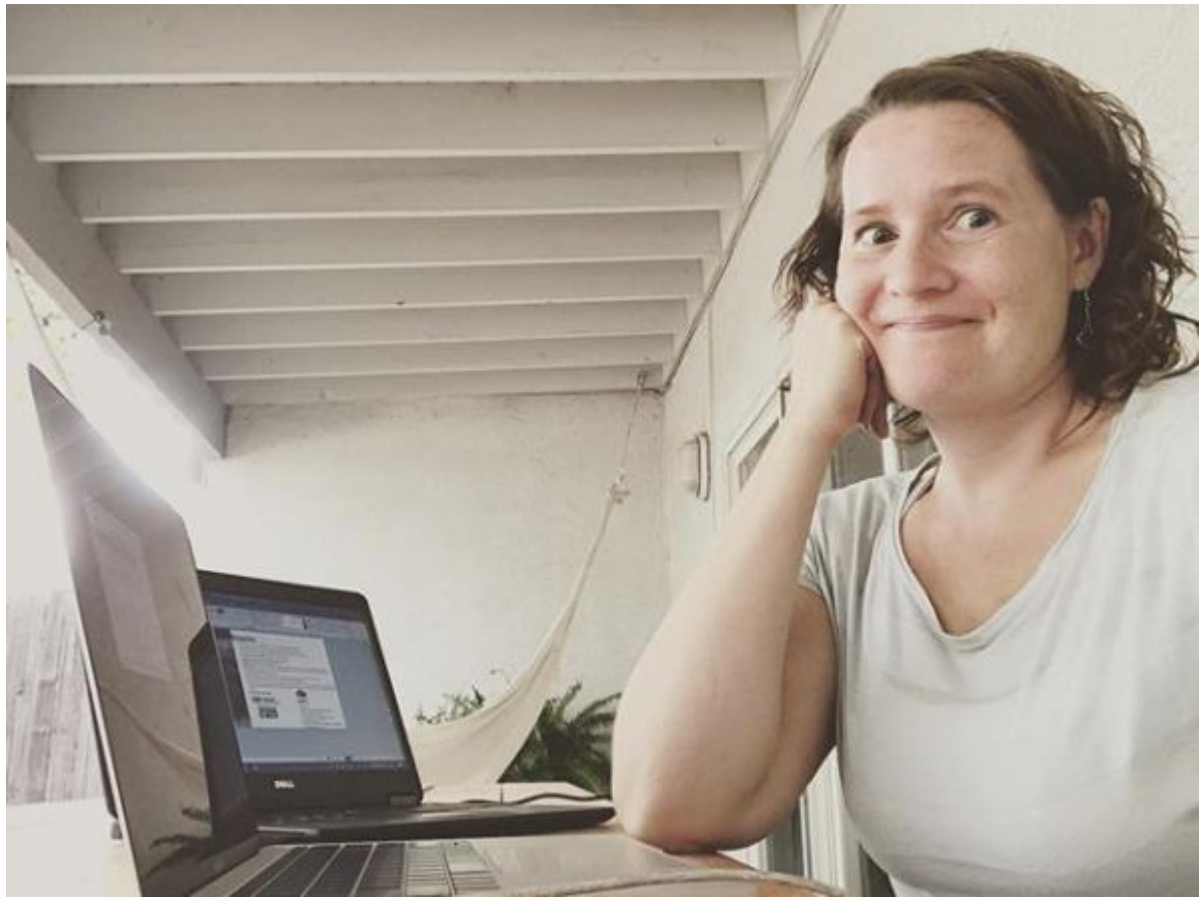

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Beyond the Pill

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