MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Premenstrual Dysphoric Disorder (PMDD)

Laura Fagioli Petrillo, M.D.

Director of Training, The Ammon-Pinizzotto Center for Women's Mental Health

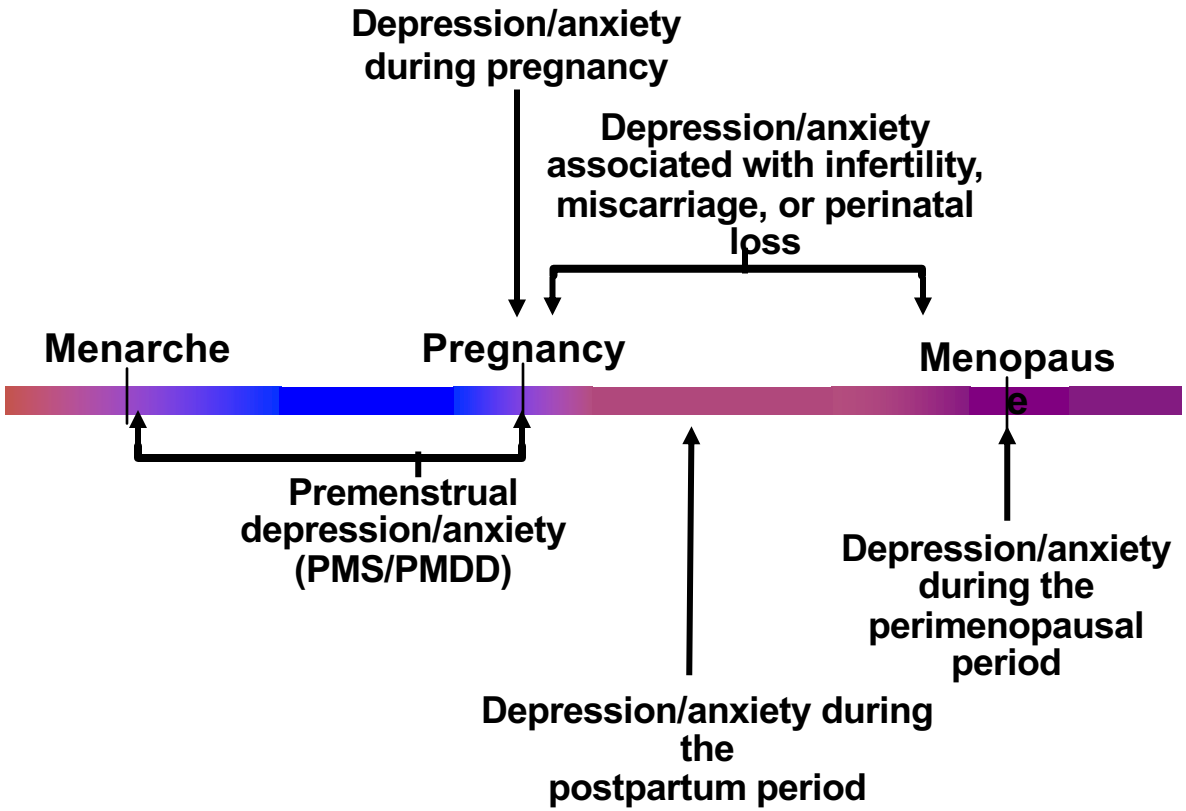
Massachusetts General Hospital

Instructor in Psychiatry, Harvard Medical School

Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Depression and Anxiety Across the Female Reproductive Cycle

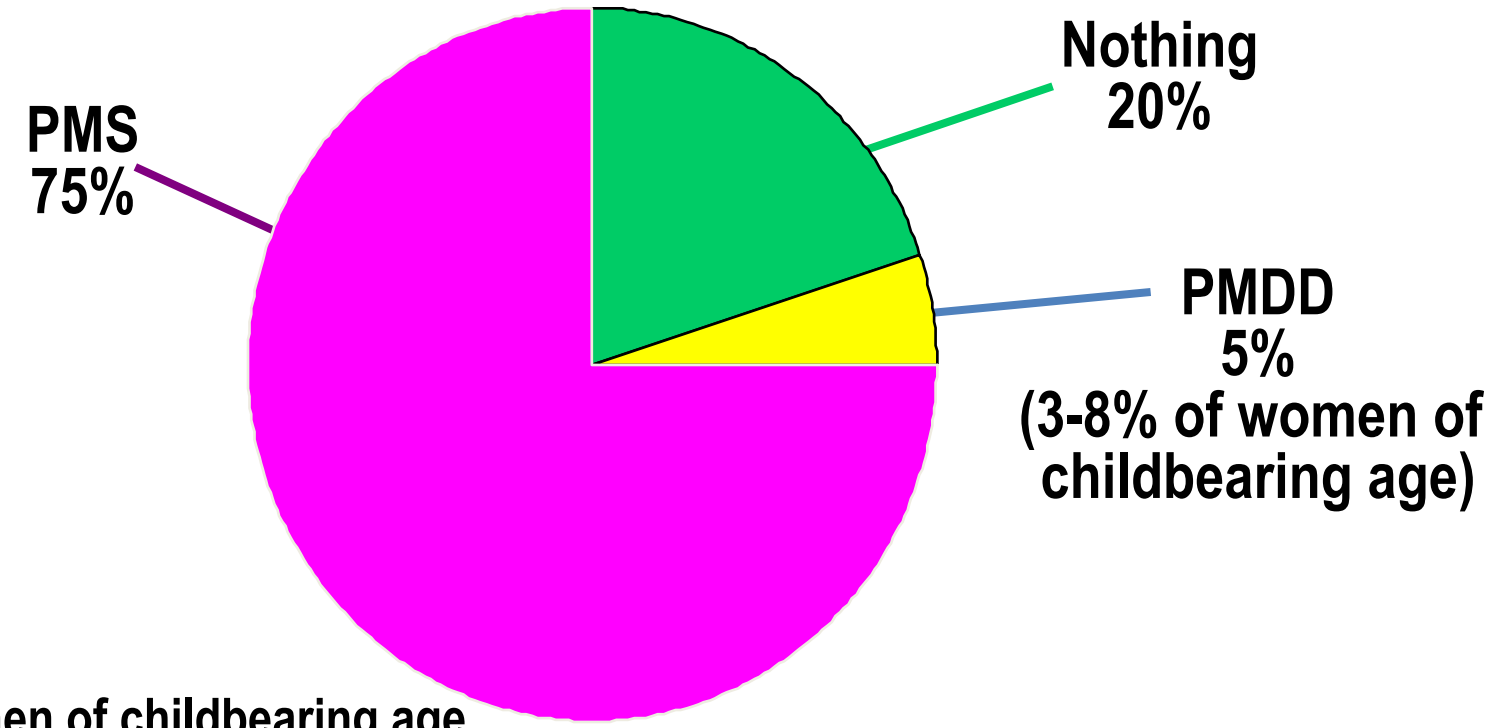


Premenstrual Mood Changes

- Majority of reproductive age women report unpleasant symptoms around the time of menstruation
  - Physical and psychological symptoms
  - "More emotional"
  - Minimal effect on functioning
- 2.5 million women affected annually

Clayton, *Jnl of Psych Prac*. 2008;14:13-21.
Winer & Rapkin, *Jnl Reproductive Med*. 2006;51(4): 339-347.

Prevalence of Premenstrual Conditions



100%=all women of childbearing age.

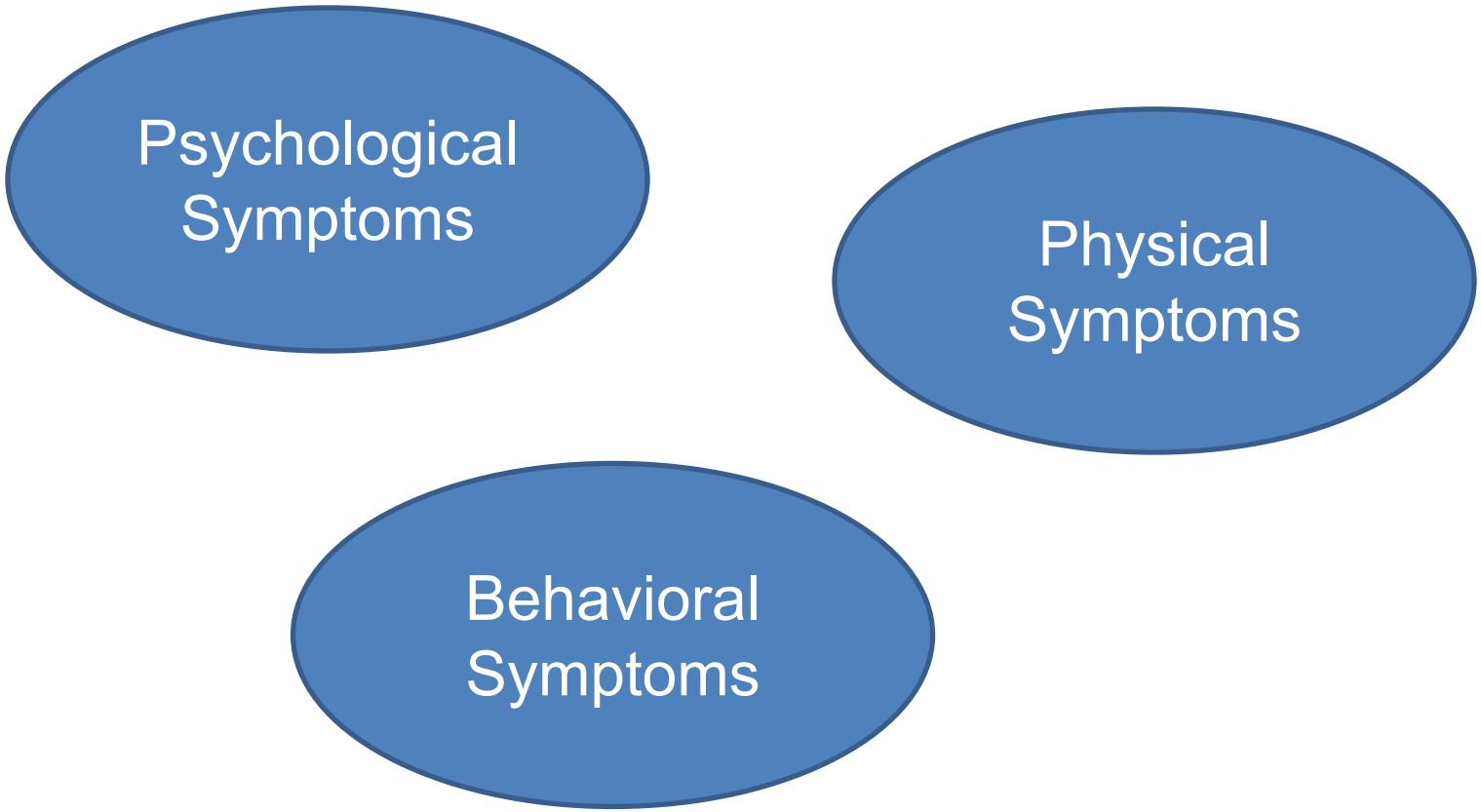
Haskett RF. *Prog Neuropsychopharmacol Biol Psychiatry.* 1987;11(2-3):129-135.
Johnson SR, et al. *J Reprod Med.* 1988;33(4):340-346.
Rivera-Tovar AD, Frank E. *Am J Psychiatry.* 1990;147(12):1634-1636.
Ramcharan S, et al. *J Clin Epidemiol.* 1992;45(4):377-392.

Premenstrual Syndrome (PMS)

- Pattern of physical, emotional and behavioral symptoms occurring 1-2 weeks before menstruation
- Symptoms remit with the onset of menstruation
- 30-80% of women
- Significant in 3-8% of women
- Occurs cross-culturally

Wittchen HU, Becker E, Lieb R, et al. *Psychol Med*. 2002;32:119-132.

PMS Symptoms



PMDD - DSM-V Criteria

- Criterion A: in most menstrual cycles during the past year, at least 5 of 11 symptoms (including at least 1 of the first 4 listed) were present:
  - Markedly depressed mood, hopelessness, or self-deprecating thoughts
  - Marked anxiety, tension, feelings of being “keyed up” or “on edge”
  - Marked affective lability
  - Persistent/marked anger or irritability or interpersonal conflicts
  - Decreased interest in usual activities
  - Subjective sense of difficulty in concentrating
  - Lethargy, easy fatigability, or marked lack of energy
  - Marked change in appetite, overeating, or specific food cravings
  - Hypersomnia or insomnia
  - A subjective sense of being overwhelmed or out of control
  - Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain
- The symptoms must have been present for most of the time during the last week of the luteal phase, begun to remit within a few days of the onset of menstrual flow, and absent in the week after menses

DSM-V Criteria

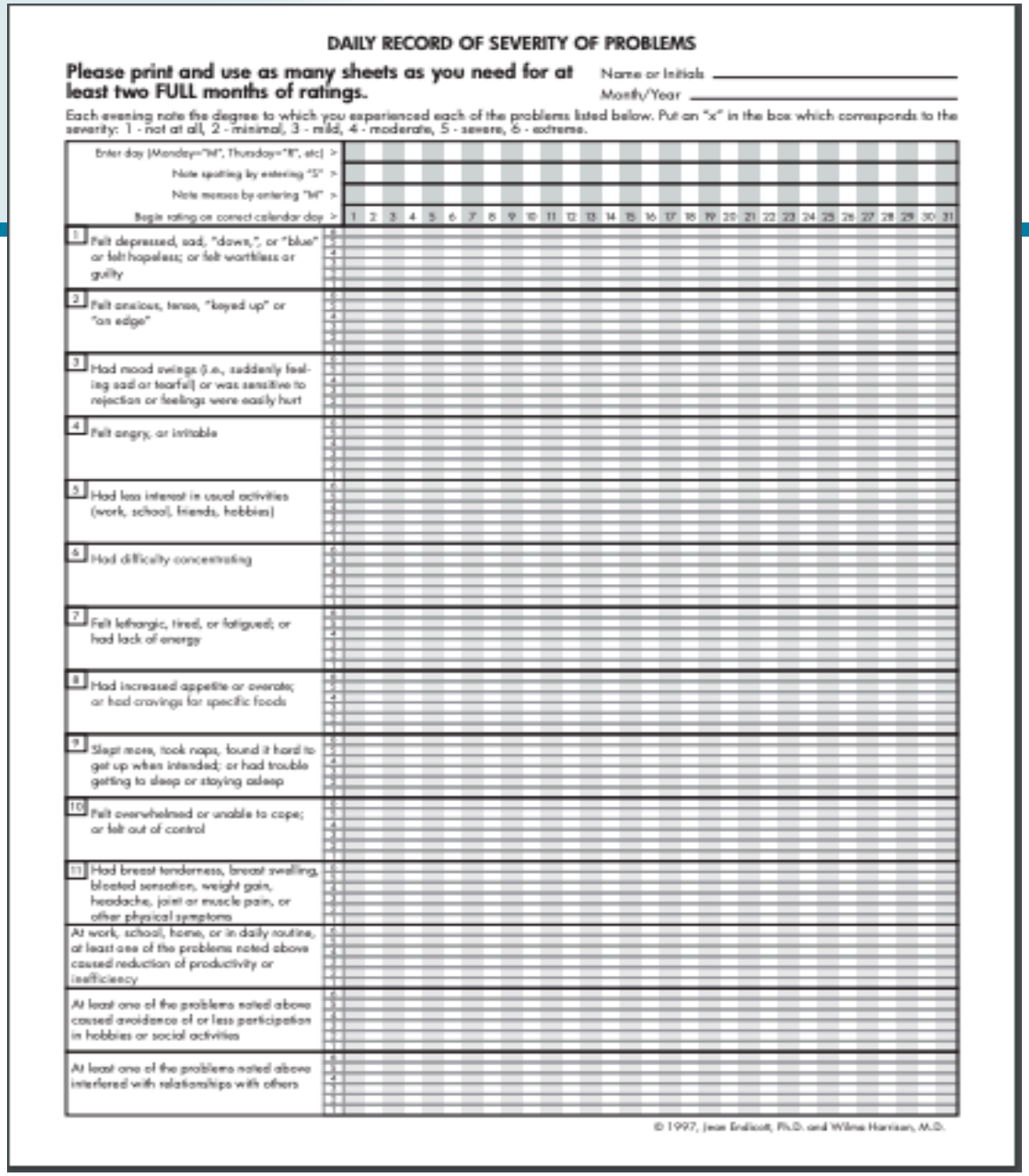
- Criterion B is that the symptoms must be severe enough to interfere significantly with social, occupational, sexual, or scholastic functioning.
- Criterion C is that the symptoms must be discretely related to the menstrual cycle and must not merely represent an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder.
- Criterion D is that criteria A, B, and C must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic menstrual cycles. The diagnosis may be made provisionally before this confirmation.

Premenstrual Exacerbation (PME)

- Mood disorders can worsen premenstrually
- PMDD vs. PME
- 40% of women screened for PMDD have an underlying mood disorder with PME
- Charting to determine cyclicity of symptoms

Bailey & Cohen. *J Women's Health Gender Based Med*. 1999;8(9):1181.

Prospective Rating Chart – Daily Record of Severity of Problems
DRSP



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

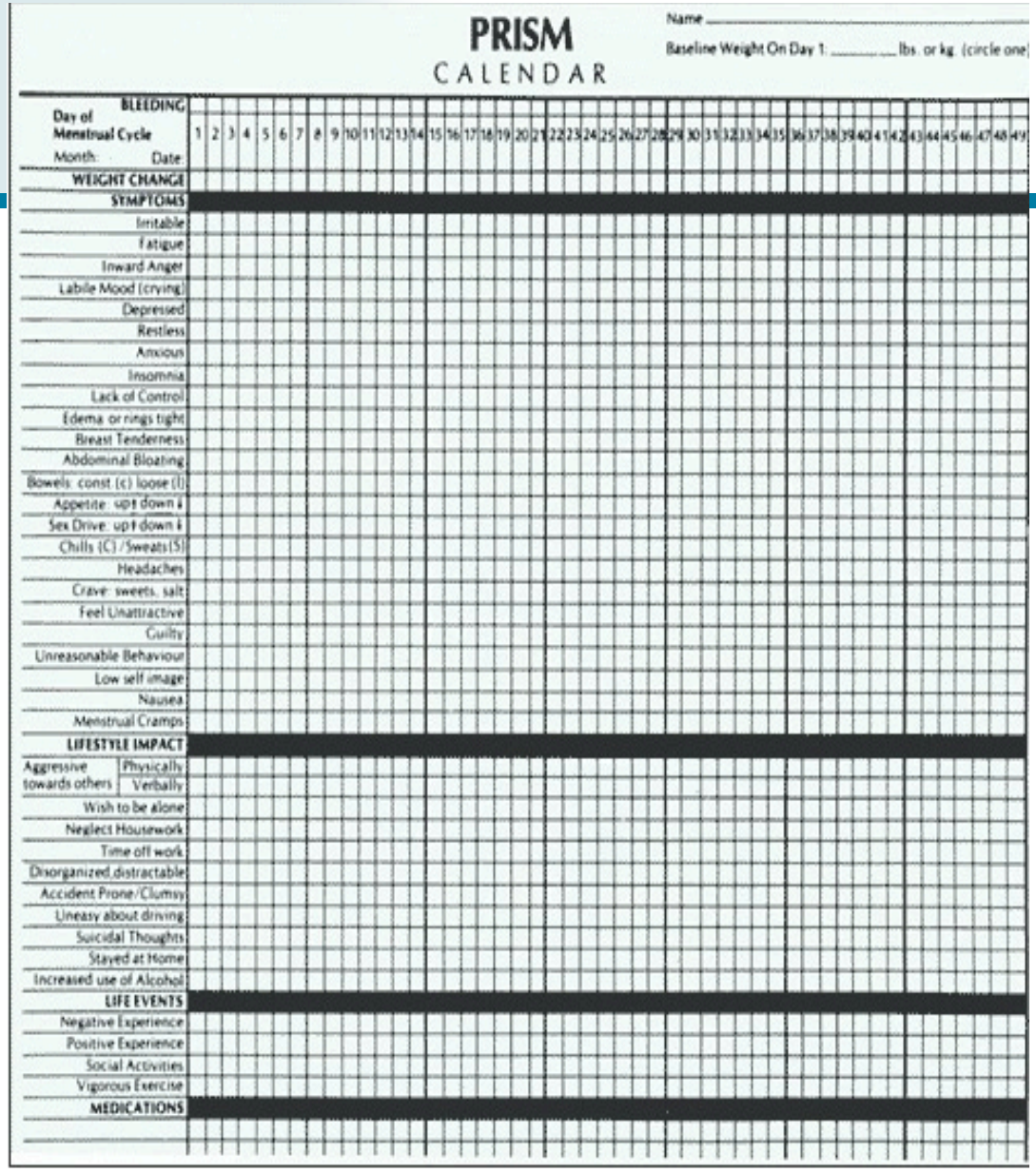
1	Felt depressed, sad, "down,", or "blue" or felt hopeless; or felt worthless or guilty
2	Felt anxious, tense, "keyed up" or "on edge"
3	Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt
4	Felt angry, or irritable
5	Had less interest in 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

© 1997, Jean Endicott, Ph.D. and Wilma Harrison, M.D.

Borenstein JE, Dean BB, Yonkers KA, Endicott J. *Obstet Gynecol*. 2007;109(5):1068-1075.

Endicott J, Nee J, Harrison W. *Arch Women's Ment Health*. 2006;9(1):41-49.

Prospective Rating Chart – Prospective Record of the Severity of Menstruation PRISM


PRISM
CALENDAR
Name
Baseline Weight On Day 1: ____ lbs. or kg (circle one)
BLEEDING
Day of Menstrual Cycle
Month: Date:
WEIGHT CHANGE
SYMPTOMS
Irritable
Fatigue
Inward Anger
Labile Mood (crying)
Depressed
Restless
Anxious
Insomnia
Lack of Control
Edema or rings tight
Breast Tenderness
Abdominal Bloating
Bowels: const (c) loose (l)
Appetite: up↑ down↓
Sex Drive: up↑ down↓
Chills (C) / Sweats (S)
Headaches
Crave: sweets, salt
Feel Unattractive
Guilty
Unreasonable Behaviour
Low self image
Nausea
Menstrual Cramps
LIFESTYLE IMPACT
Aggressive towards others: Physically, Verbally
Wish to be alone
Neglect Housework
Time off work
Disorganized, distractable
Accident Prone/Clumsy
Uneasy about driving
Suicidal Thoughts
Stayed at Home
Increased use of Alcohol
LIFE EVENTS
Negative Experience
Positive Experience
Social Activities
Vigorous Exercise
MEDICATIONS

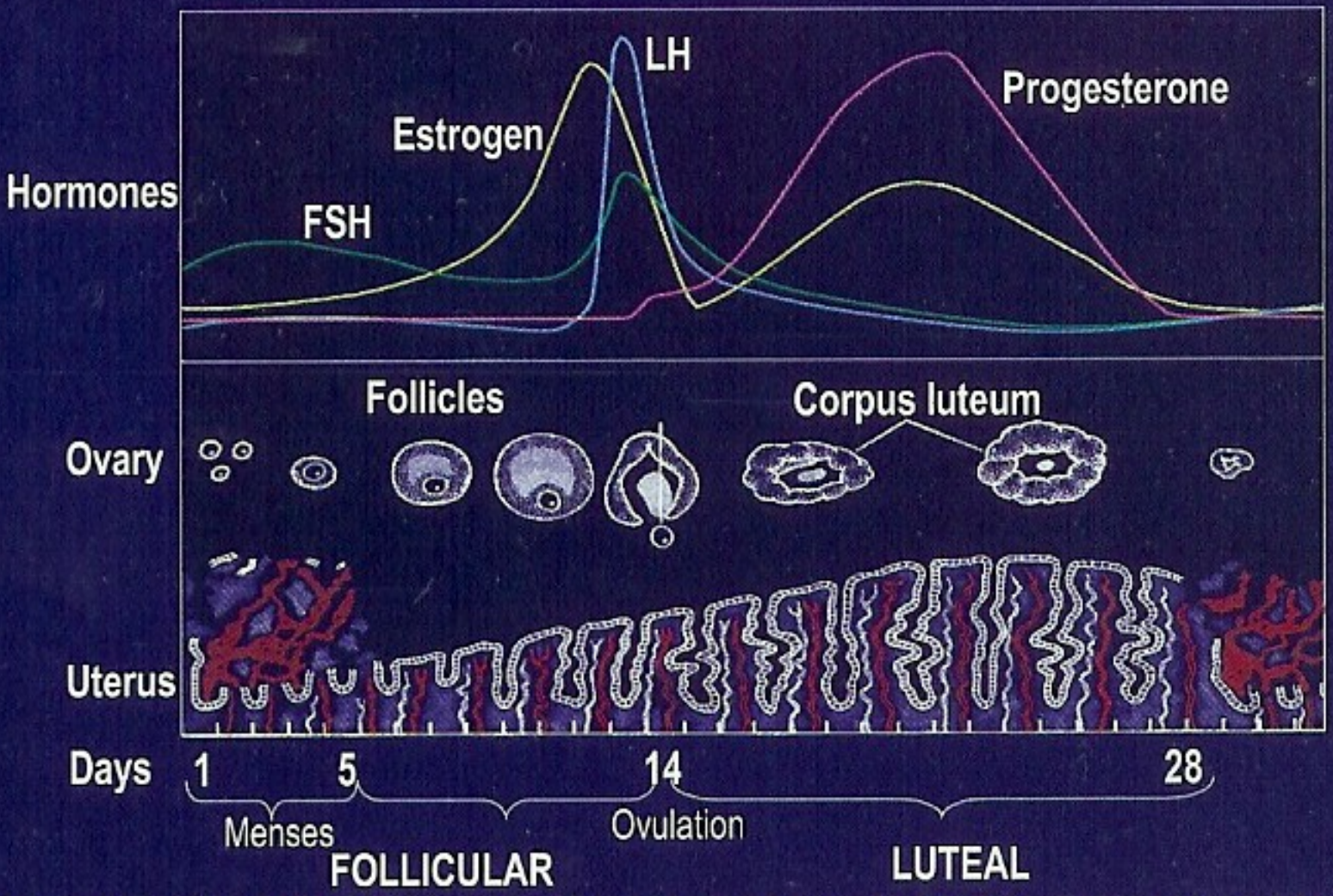
Many additional charts and apps:

Premenstrual Symptoms Screening Tool (PSST)

Calendar of Premenstrual Experiences (COPE)

Renske C. et al. *J Affect Disord.* 2016;189:43–53

The Menstrual Cycle



Adapted from Solomon EP, Davis PW. *Human Anatomy and Physiology*. Philadelphia: Sanders College; 1982.

Risk Factors for PMDD and PMS

- Family history of PMS and PMDD[1,2]
- History of postpartum depression[3]
- Major depression past[3,4] or future[5]
- Trauma history[6]

1. van den Akker OB, et al. *Acta Genet Med Gemellol (Roma).* 1987;36(4):541-548. 2. Kendler KS, et al. *Psychol Med.* 1992;22(1):85-100. 3. Warner P, et al. *J Affect Disord.* 1991;23(1):9-23. 4. Bancroft J, et al. *Psychosom Med.* 1994;56(3):225-231. 5. Graze KK, et al. *Acta Psychiatr Scand.* 1990;81(2):201-205. 6. Perkonigg A, Yonkers KA, Pfister H, et al. *J Clin Psychiatry*. 2004;65:1314-1322.

PMS/PMDD Longitudinal Course

- Women seek treatment in their late 20s/early 30s
- Peaks around 30-39 years old[1]
- Physical/mood symptoms stable from cycle to cycle[2]
- Diagnosis appears stable over time[3]
- **Chronic course** although symptoms may improve during suppression of the ovarian cycle (lactational amenorrhea, pregnancy, post-menopause)[4]

1Johnson. *Clin Obstet Gynecol.* 1987;30:369.
2Block. *Am J Psychiat.* 1997;154:1741.
3Roca et al. *J Clin Psychiatry.* 1999;60:763.
4Reid RL. Endotext [Internet]. MDText.com, Inc.; 2017-.

Diversity Research and PMDD

- Most studies do not involve diverse populations
- Unclear whether the prevalence varies by race
- Prevalence among Black women may be lower per one study[1]
- Among non-white populations of US women (Asian, Latinx, Black), perceived discrimination may be a risk factor[2]
- Rates of severe PMS and PMDD in East Asian women were lower than Western women[3-4]

1. Pilver CE, et al. *Psychol Med*. 2011;41(8):1741-1750
2. Pilver CE, et al. *J Womens Health (Larchmt)*. 2011;20(6):923-931
3. Takeda T, et al. *Arch Womens Ment Health*. 2006;9(4):209-212
4. Schatz DB, et al. *Int J Psychiatry Med*. 2012;43(4):365-380.

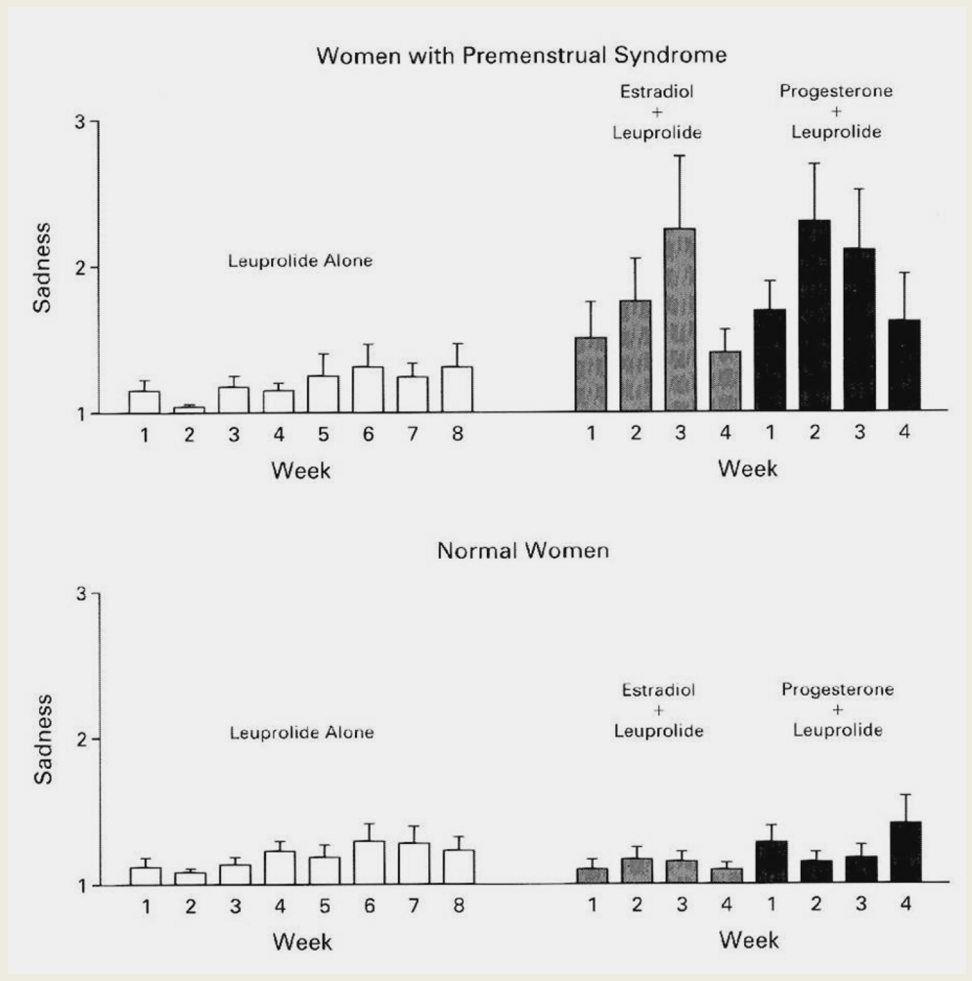
Pathophysiology

- No clear evidence of “hormonal dysregulation”
- Levels of progesterone and estradiol remain within normal range
- PMS/PMDD may represent an abnormal response to normal fluctuations of gonadal steroids

Schmidt et al., *American Journal of Psychiatry*:2017;174(10), 980-989.

Hormonal Basis of PMDD

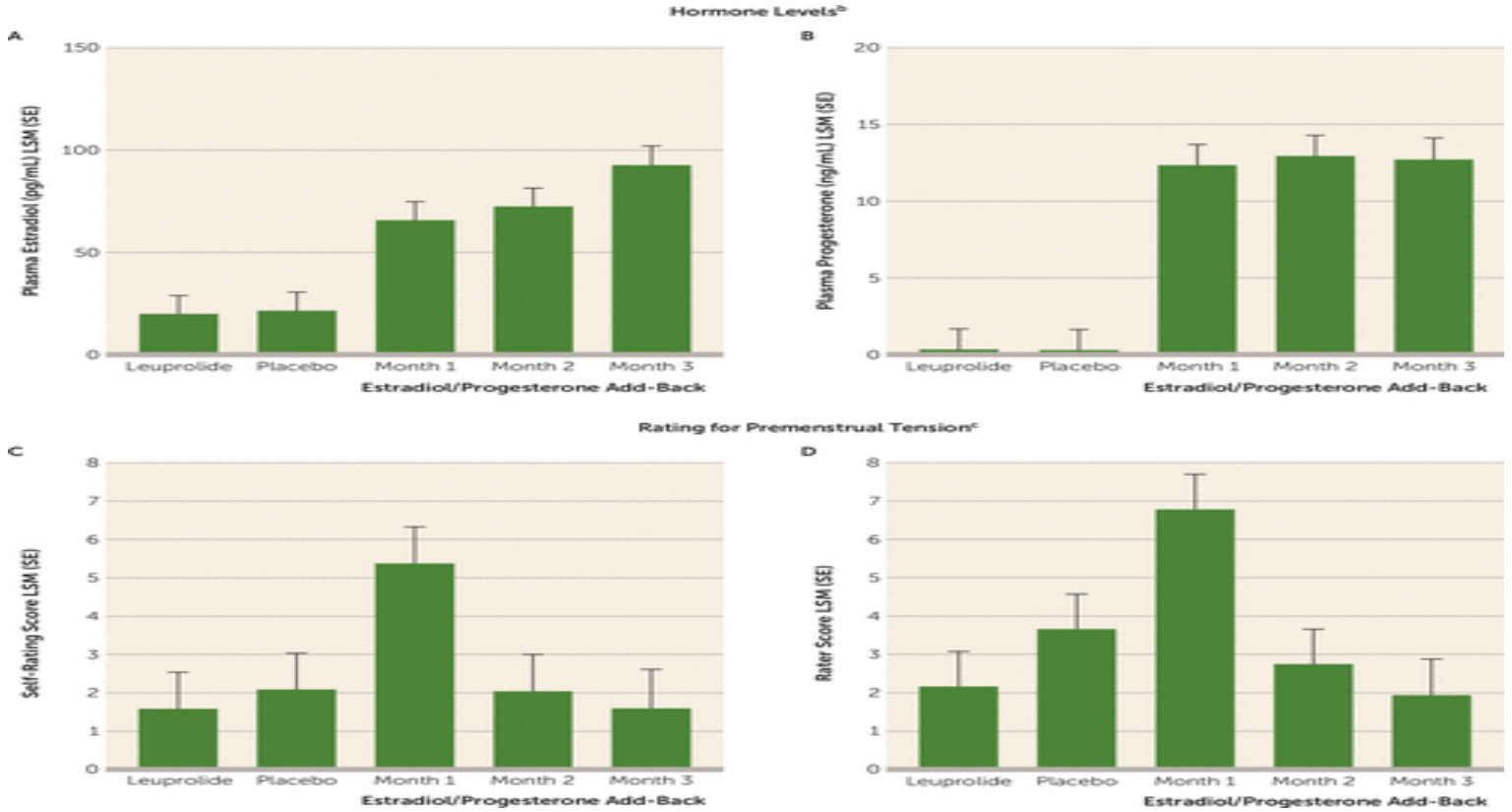
- Differential sensitivity to normal changes in estrogen and progesterone
- GnRH agonists are effective therapy
  - Eliminate hormonal fluctuation
  - PMS re-occurs with add-back therapy



GnRH = gonadotropin-releasing hormone.

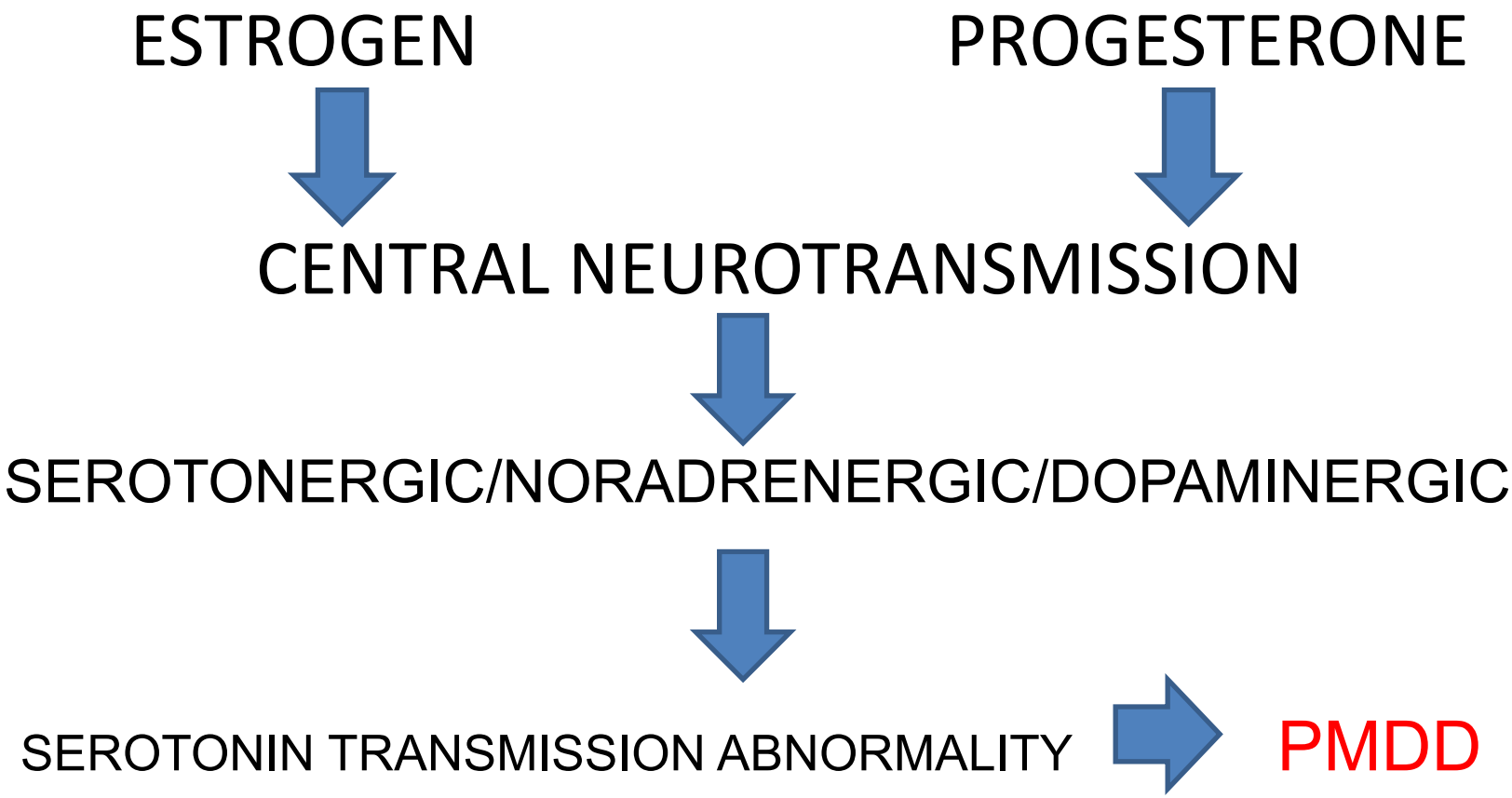
Schmidt et al. *N Engl J Med.* 1998;338:209.

Hormonal Basis of PMDD



Schmidt PJ, Martinez PE, Nieman LK, et al. *Am J Psychiatry*. 2017;174:980-989.

Pathophysiology



Pathophysiology

- Role of gamma amino-butyric acid (GABA)
  - Allopregnanolone enhances effects of GABA, acts as an anxiolytic
- Paradoxical effect of allopregnanolone mediated via the GABA-A receptor => neg mood symptoms[1]
- PMDD = greater ALLO/prog ratio vs. controls in luteal phase[2]
- Treatment with ALLO antagonist during the luteal phase reduced PMDD scores on the DRSP[3]

1.Bäckström T, et al. *Prog Neurobiol*. 2014;113:88-94.
2.Girdler SS, et al. *Biol Psychiatry*. 2001;49(9):788-797.
3.Bixo M, et al. *Psychoneuroendocrinology.* 2017;80:46-55.

Pharmacologic Treatment

SSRIs are first line treatment in patients without bipolar disorder

- fluoxetine
- sertraline
- controlled release paroxetine

Antidepressants with serotonergic activity

- venlafaxine
- duloxetine
- clomipramine

Sundblad et al. *Acta Psychiatr Scand*. 1992;85:39-47.
Freeman et al. *Obstet Gynecol*. 2001;98:737-44.
Ramos & Hara. *Int J Neuropsychopharmacol.* 2009;12(8):1081-8.

Antidepressant Dosing

- Continuous
  - Steady dose throughout the month
- Intermittent
  - Luteal phase (day 14 to onset of menstruation)
- Symptom onset
  - Women with irregular cycles
- Luteal phase increase
  - Continuous with luteal phase “bump up”

SSRI Treatment Considerations

- Start with low dose
- If no response after first cycle, increase for second cycle and continue for 2-4 cycles
- If unsatisfactory response, consider alternative SSRI and/or change dosing
- If no response to 2 SSRIs, may try a 3rd or SNRI/TCA; if incomplete response, consider adjunctive symptom targeted treatment

Adjunctive Psychopharmacologic Treatment

- Benzodiazepines
  - Alprazolam – mixed results
- Buspirone
  - Mixed results; benefit may be modest
- Gabapentin
  - Anecdotally helpful
- Quetiapine SR
  - Modest benefit
  - Small sample size

Schmidt PJ, Grover GN, Rubinow DR. *Arch Gen Psychiatry*. 1993;50(6):467-473.
Harrison WM, Endicott J, Nee J. *Arch Gen Psychiatry*. 1990;47(3):270-275.
Freeman EW. *CNS Drugs*. 2004;18(7):453-468.
Jackson C, Pearson B, Girdler S, et al. *Hum Psychopharmacol*. 2015;30(6):425-434.

Duration of Treatment in PMDD

- Optimal length of treatment is unclear
- Many women relapse when they stop treatment–as early as 1 to 2 cycles[1-4]
- Some studies suggest 12 months of treatment, then stop and observe or switch to intermittent treatment[1-5]
  - If using intermittent treatment, discontinue after a year
  - If symptoms recur, resume treatment until pregnancy or menopause
- Chronic treatment may be necessary

1.de la Gandara Martin JJ. *Actas Luso Esp Neurol Psiquiatr Cienc Afines.* 1997;25(4):235-242. 2. Pearlstein TB, Stone AB. *J Clin Psychiatry.* 1994;55(8):332-335.3. Elks ML. *South Med J.* 1993;86(5):503-507. 4. Freeman EW, et al. *Am J Psychiatry.* 1992;149(4):531-533. 5. Freeman EW, et al. *Arch Gen Psychiatry*. 2009;66(5):537-544.

Oral Contraceptives (OC)

- Evidence from double-blind, randomized, placebo-controlled trials supports use of some OCs for treatment of PMDD
- Progesterone only pill unlikely to be helpful[1-3]
- OCs containing drospirenone may be more effective
  - 4 day vs 7 day placebo
- Comparison drospirenone vs other progestins

1.Ford O, et al. *Cochrane Database Syst Rev*. 2006;(4):CD003415.
2.Wyatt K, et al. *BMJ.* 2001;323:776-780
3.Freeman E, et al. *JAMA*. 1990;264(3):349-353.

OC Dosing

- Cyclic
  - 21-24 days active pill, 4-7 days placebo
- Continuous
  - Consecutive pill packs without a placebo
  - Efficacy greater than cyclic dosing
- Begin with cyclic dosing
- Move to continuous dosing if symptoms persist

<u>Always consider medical risks of OCP</u>

Freeman et al. *Contraception.* 2012;85(5): 437-445
Skovlund et al. *Am Jnl Psychiatry*. 2018;175(4): 336-342

Gonadotropin-Releasing Hormone Agonists

- Leuprolide – depot injection every 1-3 months
- Buserelin – intranasal spray daily
- PLUS Add-back of estrogen, progestin or both
- Down-regulate gonadotropin receptors in pituitary to create a hypogonadotropic state
- Treatment usually restricted to six months
- Long term effects are unknown

Mortola JF et al. *J Clin Endocrinol Metab.* 1991; 72: 252A–252F
Ripps BA et al. *J Reprod Med*. 2003;48:761–766.
Wyatt et al. *Br J Obstet Gynaecol*. 2004; 111: 585-593

Gonadotropin-Releasing Hormone Agonists

- Double-Blind, placebo-controlled trials
  - Several show superiority of GnRH agonists over placebo[1–8]
  - Some show GnRH agonists equal to placebo[9,10]
  - Not first line
    - Consider after failure of non-pharmacologic agents, SSRIs and OCs

1. Brown CS, et al. *Obstet Gynecol.* 1994;84(5):779-786. 2. Freeman EW, et al. *Psychopharmacol Bull.* 1997;33(2):303-309. 3. Hammarback S, Backstrom T. *Acta Obstet Gynecol Scand.* 1988;67(2):159-166. 4. Hussain SY, et al. *Gynecol Endocrinol.* 1992;6(1):57-64. 5. Leather AT, et al. *Gynecol Endocrinol.* 1999;13(1):48-55. 6. Muse KN, et al. *N Engl J Med.* 1984;311(21):1345-1349. 7. Schmidt PJ, et al. *N Engl J Med.* 1998;338(4):209-216. 8. Sundstrom I, et al. *Acta Obstet Gynecol Scand.* 1999;78(10):891-899. 9. Helvacioglu A, et al. *J Reprod Med.* 1993;38(11):864-870. 10. West CP, Hillier H. *Hum Reprod.* 1994;9(6):1058-1063.

Non-Pharmacologic Treatment

- Mood Charting
- Lifestyle Modification
  - Diet, exercise, sleep
- Psychotherapy
- Nutritional Supplements
- CAM

Andrzej, M & Diana, J. *Maturitas*. 2006;55:S47-S54.
Samadi, Z., et al. *Iran J Nurs Midwifery Res.* 2013;18:14–19.

Nutritional Supplements

- Calcium (1200 mg daily)
- Vitamin B6 (50-100 mg daily)
- Magnesium (200-460 mg daily)
- Vitamin E (400 IU daily)

Thys-Jacobs S et al. *Am J Obstet Gynecol.* 1998;179: 444–52. Chocano-Bedoya P et al. *The Am Jnl Clin Nutr.* 2011;93(5):1080-1086. Fathizadeh N et al. *Iran J Nurs Midwifery Res.* 2010;15:401-5. Shobeiri et al. *Obstetrics & Gynecology Science*, 2018;*60:*100–105.

Complementary and Alternative Medicine

- Omega-3
  - Limited data
  - Potential benefit
- Vitex agnus-castus (Chasteberry)
  - Data are inconclusive
  - Potential benefit
- St. John's Wort
  - Physical symptoms > emotional symptoms
  - 13-15% reduction in the level of OCP
- Light therapy
  - Inconclusive

Cerqueira RO, et al. *Arch Womens Ment Health*. 2017;20:713-719.
Verkaik S, et al. *Am J Obstet Gynecol*. 2017;217:150-166.
Jang SH, et al. *BMC Complement Altern Med*. 2014;14:11.
Sohrabi N, et al. *Complement Ther Med*. 2013;21(3):141-146.
Krasnik C, et al. *Am Jnl of Obstetrics and Gyn. 2005;193*:658-661.

Summary

- Premenstrual symptoms are common.
- A smaller percentage of women experience severe physical and emotional symptoms that interfere with their ability to function.
- Screening for these symptoms is important as it may lead to treatments that can be beneficial.
- The etiology is unclear but data are accumulating.
- Treatments can be non-pharmacologic or pharmacologic.
  - Hormonal or psychotropic
- More research is needed.