Mental Illness in Women's Health
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1

Premenstrual Dysphoric Disorder

- Premenstrual syndrome (PMS): Premenstrual emotional, behavioral and physical symptoms that remit after menses and has minor mood changes. Majority of premenstrual concerns fall under this category and do not need medical or psychiatric intervention.
- Premenstrual dysphoric disorder (PMDD): DSM5™diagnosis by definition must interfere with functioning and be associated with significant psychiatric morbidity.
- Menstrual related mood disorder (MRMD): Conditions that include PMDD and mood dysregulation related to the menstrual cycle that is clinically substantial but where the criteria for PMDD is not met.
- Premenstrual mood exacerbation (PME):May have cyclic exacerbations of other psychiatric disorder.
- Source: Steiner M, Born L. Curr Psychiatry Rep. 2002;3(6):463-469. Eisenlohr-Moul et al., AJP 2017.

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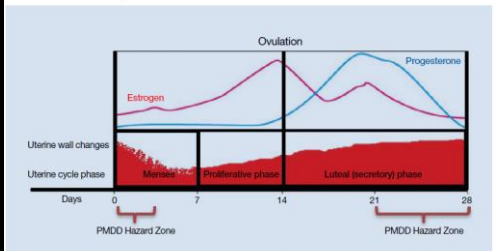
2

Figure 1

The menstrual cycle and the 'PMDD Hazard Zone'



The diagnosis of PMDD is made when a patient has at least 5 of 11 specific symptoms that occur during the week before onset of menses, improve within a few days after the onset of menses (indicated here as the "PMDD Hazard Zone"), and are minimal or absent post-menses.

PMDD: premenstrual dysphoric disorder

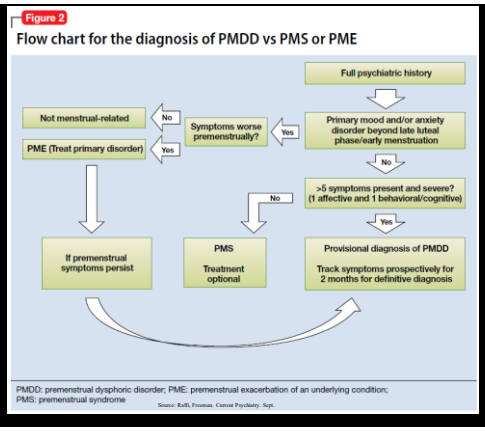
Source: Ruth, Freeman. Current Psychiatry. Sept. 2017.

3

Making the Diagnosis

- Patient has at least 5 of the 11 specific symptoms that occur before the onset of menses, improve within a few days after the onset of menses , and are minimal or absent post menses. Symptoms should be tracked prospectively for at least 2 menstrual cycles in order to confirm the diagnosis(one must be an affective symptom and another must be a behavioral/cognitive symptom.
- Affective symptoms are: a)Lability of affect ; b)Irritability, anger or increased interpersonal conflicts ; c)depressed mood, hopelessness, or self-deprecating thoughts; d)anxiety or tension, feeling "keyed up" or "on edge"
- Behavioral/Cognitive symptoms are: a)decreased interest in usual activities ; b)difficulty concentrating ; c) lethargy, low energy, easy fatiguability ; d) change in appetite, overeating, food cravings; hypersomnia or insomnia; e) feeling overwhelmed or out of control ; f) physical symptoms

4



5

Etiology of PMDD

- Abnormal response to normal hormone fluctuations.
- Women who endure it may have particular neurobiology vulnerability.
- Interplay with several factors: 1) Genetics and heritability; 2) Progesterone and Allopregnolone ; 3)Estrogen, Serotonin, and Brain Derived Neurotrophic Factor; 4) Brain Functional and Structural Differences : 5) Involvement of the Hypothalamic-Pituitary-Adrenal Axis and Hypothalamic-Pituitary-Gonadal Axis

6

Treatments for PMDD

- First line treatments: Serotonergic Reuptake Inhibitors and Oral contraceptives.
- SSRIs Highly efficacious compared to placebo including on physical, functional, and behavioral subsets.
- SSRIs effective on Luteal phase only and continuous administration.
- Combined Oral Contraceptiveshave both protesting and estrogen, recon studies in COC with drospirenone and low estrogen (approved for treating PMDD).
- COC studies show low response rate and further studies with long term study to separate from placebo and also not safe in women 35+ who smoke.

7

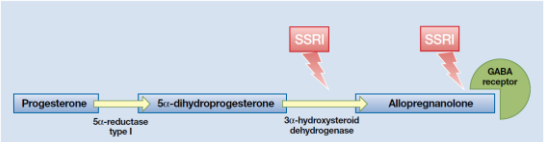
Antidepressant Dosing Strategies

- Relatively lower doses may be enough
- Continuous
- Continuous with higher dosing premenstrually.
- Intermittent Scheduled
- Intermittent PRN

8

Figure 4

Conversion of progesterone to ALLO and the SSRI influence



SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO as shown here. This is one possible mechanism by which they could be helping to alleviate PMDD symptoms.

ALLO: allopregnanolone; GABA: γ-aminobutyric acid; PMDD: premenstrual dysphoric disorder; SSRI: selective serotonin reuptake inhibitor

Source: Rafii, Freeman. Current Psychiatry. Sept. 2017.

9

PMDD Non-Medication Treatments

- Light Therapy
- Exercise
- Calcium
- Omega -3 Fatty Acids
- Diet

10

Treatment Strategies for PMDD, Premenstrual Mood Exacerbation

Treatment	How to add	Comments
Antidepressants First line	Monotherapy: Intermittent or daily Dosing: Can increase dose premenstrually	Serotonergic antidepressants, SSRIs best studied
Oral contraceptives First line	Variable results—monotherapy or adjunctive therapy	Results vary between women and OCP preparation; watch for OCP dysphoria, contraindicated in smokers over 35
Exercise	Adjunctive strategy	
Nutrition— general, decrease fat	Adjunctive strategy	Overall improved nutrition, decrease saturated fat, increased fruit, vegetables
Omega-3 fatty acids	Adjunctive strategy	1 to 3 g EPA+DHA per day
Calcium	Adjunctive strategy	1,200-1,500 mg calcium per day

11

Depression and Anxiety During Pregnancy

- Risks of untreated depression during pregnancy: May negatively affect maternal weight gain. May increase the risk of low birth weight, prematurity, and small for gestational age. Neonatal behavioral differences. May lead to less compliance with prenatal care.
- Panic disorders and Pregnancy: Affects 2.5 to 4% of pregnant women. Course appears to be variable and research suggests some women may particularly vulnerable to relapse during pregnancy. Some studies suggest increased risk of new onset panic disorder in postpartum women.
- Perinatal GAD: Affects 9-10% of women during pregnancy as well as postpartum. Highest risk in the first trimester. May be challenging to differentiate GAD from normal worry.

12

- OCD: Prevalence of 3.5% in pregnant women. Higher risk of OCD after childbirth up to 9% of postpartum women. 8 % of women with preexisting OCD report worsening.

13

Treatment of MDD During Pregnancy

- Psychotherapy is first like for mild to moderate MDD
- Lifestyle component" Nutrition, weigh maagenemtn, prenatal care, childbirth education, treatment of SUDs
- If prior hx of MDD encourage period of euthymia, if sustained remission consider tapering off, if more recent or ongoing signs and symptoms of MDD consider remaining/optimizing medication.
- For severe MDD medication is first line.
- Take into account patient preferences and previous course of illness.
- Medication selection should be based on known safety information.

14

- Absolute risk of treating depression with SSRI's is small
- Reproductive safety data on SSRI exceeds what is known about other medications in pregnancy.
- No evidence of increased risk for malformation or cardiovascular malformations in pregnant women exposed to SSRIs
- Antidepressant exposure and risk of ASD: meta review and meta analysis done initially showed association that disappeared once confounding variables and maternal history of mental illness.
- Bupropion and pregnancy: No clear pattern of birth deffects. Small study showed no evidence of increased malformations compared to other antidepressants. No malformations/cardiovascular malformations seen in large study

15

Treatment of anxiety during pregnancy

- Psychotherapy
- Massage, acupuncture, meditation.
- Limit internet.
- Antidepressants as first like for moderate to sever anxiety disorders.
- Judicious use of benzodiazepine and hypnotics.

16

Postpartum Mood and Anxiety Disorders

- Postpartum Blues
- Postpartum Depression (Peripartum onset in DSM5™, onset within 4 weeks of delivery)
- Postpartum Psychosis.
- Postpartum Episodes of Bipolar Disorder.
- Postpartum Anxiety Disorders or Symptoms.

17

Postpartum Depression

- 10-15% of women experience MDD after delivery(25-40% if they had prior hx of MDD).
- Similar signs and symptoms to non puerperal MDD.
- Impairment of functioning.
- Obsessions and compulsions are often present
- Predictors: History of depression, depression in pregnancy, anxiety in pregnancy, stressful life events, marital dissatisfaction, child care stress, inadequate social support, difficult infant temperament, low self esteem, family history of postpartum depression.

18

PPD treatment

- Moderate to severe depression should consider role of antidepressants and discuss risks/benefits with mother.
- Use lowest effective dose.
- Consultation with perinatal/reproductive psychiatry specialists as needed.
- Non pharmacological strategies include maximizing social support, psychoeducation to mother and family, group therapy and support groups, interpersonal therapy, cognitive behavioral therapy (6 session CBT similar results to Fluoxetine treatment at 6 weeks)

19

Antidepressant Trials for the Treatment of PPD

Study	Design and Size	Medication studied, result
Appleby et al., 1997	Placebo-controlled, N=87 CBT studied in same trial	Fluoxetine - superior to placebo
Yonkers et al, 2008	placebo controlled, N=70	Paroxetine - not superior to placebo)
Wisner et al., 2006	RCT, Setraline vs. Nortriptyline, N=109	Sertraline vs. Nortriptyline - no significant difference
Hantsoo et al., 2013	Placebo-controlled RCT, N=36	Setraline- superior to placebo
Bloch et al., 2012	N=40, all received brief psychodynamic therapy, RCT to sertraline or placebo	Both groups improved – no significant difference for sertraline vs. placebo
Sharp et al., 2010	RCT, AD selected by general practitioner or counseling, N=254	Antidepressants- superior to placebo
Misri et al., 2012	Open trial, N=15	Citalopram – open study
Misri et al., 2004	N=35, all received parox, half randomized to CBT also	Paroxetine – no control group
Stowe et al., 1995	Open-label; N=21	Sertraline – open study
Cohen et al., 1997	Open-label; N=19	Venlafaxine- open study
Suri et al., 2001	Open-label; N=6	Fluvoxamine - open
Nonacs et al., 2005	Open-label; N=8	Bupropion - open

20

Breastfeeding and Antidepressants

Fluoxetine	Due to long half life, may be more likely to be found at detectable levels in infant serum, especially at higher doses. • Reasonable for use if a woman has had a good previous response to it and reasonable to consider if used during pregnancy.
Sertraline	• Consistent reports of low levels of exposure, relatively large amount of study
Citalopram, escitalopram	• Less systematic study of mom-baby pairs compared with sertraline and paroxetine, observed low levels of exposure to infant via breastfeeding
Paroxetine	• Consistent reports of low levels of exposure, relatively large amount of study • Use limited by commonly experienced withdrawal symptoms, maybe more sedating than other SSRIs
Bupropion	• Paucity of systematic study; a few case reports in older infants that demonstrate low levels of exposure via breastfeeding • May be advantageous in smokers • Reasonable for use if women have had good previous response • One case report of possible infant seizure
Venlafaxine, Desmethyl venlafaxine	• Higher levels of desmethylvenlafaxine found in breastmilk than venlafaxine • No adverse events reported
Tricyclic Antidepressants	• Considered reasonable for breastfeeding if use clinically warranted; few adverse affects in babies and generally low levels of exposure reported
Mirtazapine, nefazodone, MAOIs, duloxetine	• Systematic human lacking in the context of breastfeeding

21

Postpartum consideration in Bipolar Disorder

- Rates of recurrence after discontinuation of medication
- Similar for pregnant and non pregnant women
- More depressive episodes in pregnant women was only difference.
- Increase risk for relapse post part
- Recurrence risk greater after rapid discontinuation.

22

Postpartum Psychosis

- 1-2 per 1000 pregnancies suffer it.
- Rapid and dramatic within first two weeks
- High risk of harm to self and infant.
- Suspect Bipolar disorder

Source: Nonacs and Cohen, 1998; Jones & Craddock, 2001; Spinelli, AJP, April 2009.

23

- Estimated 4% of women with postpartum psychosis commit infanticide.
- Psychiatric emergency.
- Inpatient psychiatric treatment includes cessation of breast feeding, ruling out medical conditions (delirium), treatment with antipsychotic and mood stabilizers as well as anxiolytics and hypnotics as needed.
- Close outpatient monitoring and continuation of treatment.

24

Prevention of Postpartum Bipolar Episodes and Postpartum Psychosis

Group	During Pregnancy	With postpartum prophylaxis	Did not start postpartum prophylaxis	
Women with histories of psychosis in the postpartum only	All (29/29) remained stable off of medication during pregnancy	Started Postpartum Prophylaxis: No relapses (N=20)	Did not start Postpartum Prophylaxis: 44% relapse (N=9)	
Women with bipolar disorder	24.4% relapse: 75.6% on maintenance meds Relapse rates: 19.4% on meds 40% off meds	Of those who stayed well during pregnancy: postpartum relapse rate 7.7% on prophylaxis	Of those who stayed well during pregnancy: 20% relapse rate not on prophylaxis	60% postpartum relapse among those who experienced mood episodes during pregnancy

25

Q&A

26

- Later Pregnancy considerations: Inconsistent results regarding pulmonary hypertension newborn with SSRI exposure in late pregnancy. Reports of suspected withdrawal/toxicity after in utero exposure to SSRI, low birthweight and prematurity with no blinding or control for maternal mental health.

27