Mental Health Issues in Women Across the Reproductive Cycle

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1

Disclosure

I have no financial interests or relationships to disclose.

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2

Objectives

- At the end of this session, participants will be able to:
  - Describe how to identify and treat peripartum depression.
  - Discuss considerations of medication-based treatment in the postpartum period, particularly if the patient is breastfeeding
  - Assess and manage mood symptoms in menopausal and postmenopausal women.

3

Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

4

- Longitudinal research indicates some women demonstrate greater sensitivity to gonadal steroid shifts
- h/o severe premenstrual mood sx is associated with increased risk of perimenopause onset or relapse of MDD

Freeman EW. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psych 2004;61:62-70

5

PMS/PMDD

- Characterized by:
  - Presence of physical and/or behavioral symptoms that occur repetitively in the second half of the menstrual cycle and often the first few days of menses.
  - Symptom-free during the follicular phase. Otherwise, would be thinking more Major Depressive Disorder.
- Clinically significant PMS ~3 to 8 %
- PMDD ~ 2%

6

Treatment:

Mild symptoms (Sx)

- Lifestyle measures
  - Exercise
  - Relaxation techniques

Moderate to severe Sx

- Cognitive behavioral therapy
- Medications
  - Selective serotonin reuptake inhibitors [SSRIs]
  - Combined estrogen-progestin contraceptives (COCs)
  - Vitex agnus castus (chasteberry)?
  - Continuous versus intermittent?

7

Continuous versus Intermittent for Antidepressant Treatment

- In continuous dosing patient takes antidepressant daily vs intermittent dosing where patient takes daily during the luteal phase, i.e., from ovulation to menses only.
- Systematic review concluded that continuous and intermittent dosing had equivalent efficacy

8

Perinatal Depression

9

Pregnancy as a Risk Factor?

- Overall, population prevalence rates of depression for women are similar before and during pregnancy
  - General prevalence post puberty: 10-20%
  - 1st trimester prevalence: 11%
  - 2nd and 3rd trimester prevalence: 8.5%
  - But…there are things that increase risk

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.

10

Risk Factors for Perinatal Depression

- Personal or family hx of major or postpartum depression
- Gestational diabetes
- Difficulty breastfeeding
- Fetal/newborn loss
- Lack of personal or community resources
- Financial challenges
- Current anxiety
- Single
- Substance use/addiction
- Complications of pregnancy, labor/delivery, or infant's health
- Adolescence
- Unplanned pregnancy
- Major life stressors
- Violent or abusive relationship
- Isolation from family or friends

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.

11

Pregnancy as a Risk Factor for anxiety?

- There does appear to be an increased risk for anxiety symptoms worsening during pregnancy
  - Particularly seen in:
    - Generalized anxiety disorder
      - 8.5% prevalence in pregnancy compared to 3% in gen pop
      - Some confluence with adjustment disorder with anxious features
    - Panic disorder
      - Overall prevalence is not higher (~2%) though panic disorder symptoms may worsen in severity
- Pregnancy can be a very anxiety provoking stimulus

Thorsness KR, Watson C, LaRusso EM. Perinatal anxiety: approach to diagnosis and management in the obstetric setting. American Journal of Obstetrics & Gynecology. (2018); October: 326-345.

12

How Do You Detect Perinatal Depression?

13

Screening

Ideally..

- Once per trimester
- At postpartum visit (2 weeks if high risk, or 6-7 weeks routine visit)
- At well-child visit

Stewart DE, Vigod S. Postpartum Depression. N Engl J Med (2016);375;22:2177-2186.
T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.
Matthy S. Using the edinburgh postnatal depression scale to screen for anxiety disorders. Depression and Anxiety (2008) 25:926–931.

14

What Screening Tools to Use?

Table 1 Screening toolkit for primary care physicians

EPDS	Sensitivity = 0.86 Specificity = 0.78 For positive screen >10	5–10 minutes, self-administered, could be self-scored	www.dbpeds.org/articles/detail.cfm?TextID=485
PHQ-2	Sensitivity = 0.83 Specificity = 0.92 For positive screen >3	<1 minute, self-administered or can be asked	www.pfizer.com/pfizer/download/do/phq-9.pdf The two questions from the PHQ-9 for mood and anhedonia are used
PHQ-9	Sensitivity = 0.88 Specificity = 0.88 For positive screen >10	5–10 minutes, self-administered and self-scored	www.pfizer.com/pfizer/download/do/phq-9.pdf

Perinatal depression: Implications for child mental health. Mental Health in Family Medicine 2010;7:239-47

15

So, They Are Depressed and/or Anxious and Pregnant…Now What?

16

Summary of risk data

- With the exception of paroxetine, not thought to increased risk of major congenital malformations above the base rate in the general population (3%–5%).
- May be some small increased risk of miscarriage
- Increased risk of preterm birth
  - Average decreased gestation of 3 days
- Increased risk of low birth weight
  - ~2% lower weight
- There may be an increased risk for PPHN
  - Overall risk still < 1%
- PNAS symptoms are the most likely, concrete outcome, but these are generally mild and

17

Poor Neonatal Adaptation Syndrome (PNAS)

- Occurs in up to 30% of newborns exposed to SSRIs
- Symptoms are transient and usually mild
- Resolve with supportive care in days to weeks
- Unclear if this is due to withdrawal from SSRIs, SSRI toxicity, and/or some combination

PNAS Symptoms
Irritability
Weak cry
Poor tone
Decreased feeding
Jitteriness
Tachypnea
Respiratory distress
Temperature instability
Hypoglycemia

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Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep (2016) 18:32.

18

Benzo Use During Pregnancy

- Older data demonstrated a positive association with benzos use and cleft lip and palate
  - Newer, larger, and more well-designed studies have shown no association
- Studies have not consistently demonstrated developmental or cognitive effects in newborns and babies that are present when confounders are controlled
- Higher dosed, consistently dosed benzos in the 3rd trimester can lead to clinically significant withdrawal after delivery

Thorsness KR, Watson C, LaRusso EM. Perinatal anxiety: approach to diagnosis and management in the obstetric setting. American Journal of Obstetrics & Gynecology. (2018); October: 326-345.

19

ADHD and pregnancy

- If possible, do drug holiday through the first trimester at least
- Amphetamines are preferred due to small increased risk of cardiac malformations with intrauterine exposure to methylphenidate. (RR1.28 CI 1.0-1.64)[1]
- Study in Denmark found first-trimester exposure to ADHD rx-primarily methylphenidate found 5.1% malformations overall vs 4.6% unexposed, 2.1% cardiac malformation vs 1% unexposed = NS increase risk with methylphenidate. [2]

1. Huybrechts KF, et al. Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations: A Cohort Study From the International Pregnancy Safety Study Consortium. JAMA Psychiatry 2018; 75:167. 2. Kolding L et al. Association between ADHD Med Use in Pregnancy and Severe malformation based on Prenatal and Postnatal Dx: A Danish Registry-Based Study. J Clin Psych 82:1 Jan 2021

20

Considerations for Prescribing Medication

Suggests Medication May Not be Indicated	Suggests Medication Treatment Should be Strongly Considered
• Mild depression based on clinical assessment • No suicidal ideation • Engaged in psychotherapy or other non-medication treatment • Depression has improved with psychotherapy in the past • Able to care for self/baby • Strong preference and access to psychotherapy	• Moderate/severe depression based on clinical assessment • Suicidal ideation • Difficulty functioning caring for self/baby • Psychotic symptoms present • History of severe depression and/or suicide ideation/attempts • Comorbid anxiety diagnosis/symptoms

21

Treatment Pearls

- Antidepressant doses may well need to be increased during pregnancy to achieve consistent effect
  - Due to changes in metabolism, GFR, and volume of distribution
  - Use symptoms for guidance
- Be cautious of undertreating illness in the hope of "limiting fetal exposure"
  - Discontinuing medications prior to delivery is not a great idea
- Ensure that initial and ongoing screening includes direct questions on:
  - Suicidal thoughts
  - Thoughts of harming others, including baby
  - Symptoms of psychosis

Stewart DE, Vigod S. Postpartum Depression. N Engl J Med (2016);375;22:2177-2186.
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22

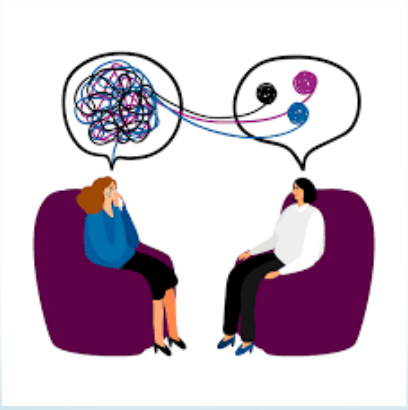
Treatment Pearls

- Screening for patient and familial history of bipolar disorder is very important
  - Average of onset of bipolar disorder (30s) coincides with common childbearing periods
- Patients with bipolar disorder have a 30-40% chance of relapse during the postpartum period
  - This is substantially reduced (~66%) with medication-based treatment
- Patients with a history of postpartum psychosis have a ~30% chance of relapse during subsequent postpartum periods
- **Psychiatric consultation is STRONGLY encouraged in these scenarios**

Wesseloo R et. al. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis. Am J Psychiatry (2016) 173;2:117-127.
Hermann A, Gorun A, Benudis, A. Lithium Usa and Non-use for Pregnant and Postpartum Women with Bipolar Disorder. Current Psychiatry Reports (2019) 21:114

23

Treatment: Psychotherapy



- First-line treatment for mild to moderate depression
- Indicated for residual symptoms, high risk of relapse
- Encourage in preconception period
- Cognitive behavioral therapy (CBT) or interpersonal psychotherapy(IPT) have been shown to be effective
- Can consider web-based CBT

24

Risk of Untreated Depression and Anxiety?

This Coin Has Two Sides

25

Risk of Untreated Depression

- Data is much less concrete and difficult to parse from other psychosocial factors and realities
  - Numerous studies have demonstrated significant impact from maternal depression, stress, and anxiety on neonatal development and outcomes
    - Preterm birth
    - Low birthweight
    - Decreased vagal tone and reactivity
    - Altered temperament and increased irritability
    - Altered attention, sleep problems, and delayed neuromotor development

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26

Risk of Untreated Depression

- Additionally:
  - Maternal depression leads to:
    - Impaired maternal infant bonding
    - Decreased desire to breastfeed
    - Shorter feeding sessions
  - Young children of untreated, depressed mothers are at increased risk for:
    - Externalizing behaviors
    - Fearful temperament and anxiety
    - Delayed motor development
    - Delayed cognitive development

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Stewart DE, Vigod S. Postpartum Depression. N Engl J Med (2016);375;22:2177-2186.

27

Risk of Untreated Depression

- Older children of mothers with untreated depression are at increased risk of:
  - ADHD
  - Depression
  - Anxiety disorders
  - Altered stress response

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.
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Stewart DE, Vigod S. Postpartum Depression. N Engl J Med (2016);375;22:2177-2186.

28

Risk of Untreated Anxiety?

- Maternal anxiety disorders lead to substantial morbidity including:
  - Sleep disruption
  - Decreased exercise
  - Poor nutrition
  - Substance use
  - Increased use of prenatal services
- Maternal anxiety disorders also impact birth outcomes:
  - Low birth weight
  - Preterm birth
  - Increased risk of preeclampsia

Thorsness KR, Watson C, LaRusso EM. Perinatal anxiety: approach to diagnosis and management in the obstetric setting. American Journal of Obstetrics & Gynecology. (2018); October: 326-345.

29

Risk of Untreated Anxiety?

- Fetal exposure to untreated maternal anxiety has been linked to:
  - Behavioral and emotional problems
  - Attentional disorders
  - Increased risk of psychiatric disorders later in life
  - Decreased gray matter volumes in areas related to learning, memory, and auditory language processing

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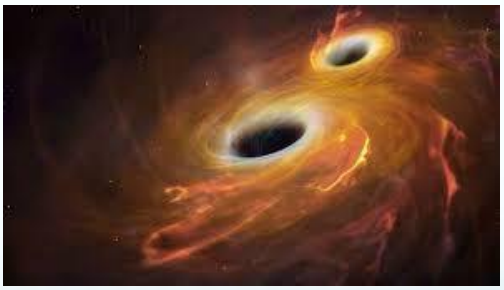
30

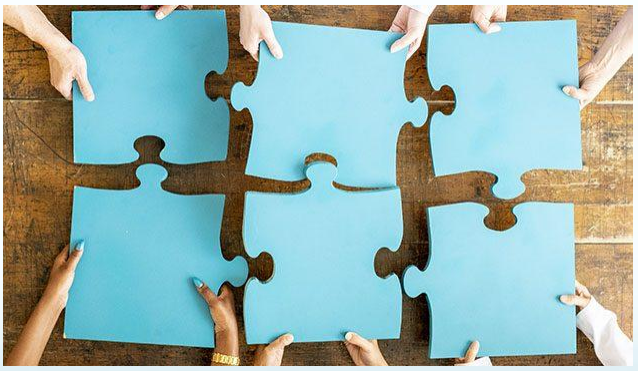
Risk of stopping antidepressants?

Women who stop their medications during pregnancy are 5 X more likely to experience a relapse in symptoms!!



31

Putting It All Together



32

Informed Consent for Antidepressant Use

- No decision regarding whether to use antidepressants during pregnancy is perfect or risk free, including not treating
- SSRIs are among the best studied class of medications during pregnancy
- Both medication and non-medication options should be considered
- Encourage non-medication treatments (e.g., psychotherapy) in addition to medication treatment or as an alternative when clinically appropriate

Risks of antidepressant use during pregnancy	Risks of under treatment or no treatment of depression during pregnancy
• Small, but inconsistent increased risk of birth defects when taken in first trimester, particularly with paroxetine • Possible transient neonatal symptoms • Low risk for persistent pulmonary hypertension • Studies do not suggest long-term neurobehavioral effects on children	• Association with preterm deliveries • Increases the risk of postpartum depression • Can make it harder for moms to take care of themselves and their babies • Can make it harder for moms to bond with their babies

- If pregnant: In your situation, the benefits of taking an antidepressant outweigh the chance of the things we just discussed.
- If lactating: SSRIs and other antidepressants are considered a reasonable treatment option during breastfeeding. The benefits of breastfeeding while taking antidepressants generally outweigh the risks.

33

So, the Baby Is Delivered…then What?

34

Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often Please complete the other questions in the same way.
☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   ☐ As much as I always could
   ☐ Not quite so much now
   ☐ Definitely not so much now
   ☐ Not at all
2. I have looked forward with enjoyment to things
   ☐ As much as I ever did
   ☐ Rather less than I used to
   ☐ Definitely less than I used to
   ☐ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   ☐ Yes, most of the time
   ☐ Yes, some of the time
   ☐ Not very often
   ☐ No, never

4. I have been anxious or worried for no good reason
   ☐ No, not at all
   ☐ Hardly ever
   ☐ Yes, sometimes
   ☐ Yes, very often

*5 I have felt scared or panicky for no very good reason
   ☐ Yes, quite a lot
   ☐ Yes, sometimes
   ☐ No, not much
   ☐ No, not at all

*6. Things have been getting on top of me
   ☐ Yes, most of the time I haven't been able to cope at all
   ☐ Yes, sometimes I haven't been coping as well as usual
   ☐ **No, most of the time I have coped quite well**
   ☐ No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   ☐ Yes, most of the time
   ☐ Yes, sometimes
   ☐ Not very often
   ☐ No, not at all

*8 I have felt sad or miserable
   ☐ Yes, most of the time
   ☐ Yes, quite often
   ☐ Not very often
   ☐ No, not at all

*9 I have been so unhappy that I have been crying
   ☐ Yes, most of the time
   ☐ Yes, quite often
   ☐ Only occasionally
   ☐ No, never

*10 The thought of harming myself has occurred to me
   ☐ Yes, quite often
   ☐ Sometimes
   ☐ Hardly ever
   ☐ **Never**

Administered/Reviewed by _____ Date _____

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786 .

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

- QUESTIONS 1, 2, & 4 (without an*) → scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.
- QUESTIONS 3, 5-10 (marked with an*) → reverse scored, with the top box scored as a 3 and the bottom box scored as 0.
  - Maximum score: 30
- Possible Depression: score of 10 or greater
- Items 3,4,&5 investigate anxiety symptoms
  - Score 6 or more on these items' screens + for anxiety

35

Prevalence

- Postpartum psychosis (0.1-0.2%)
- Postpartum blues (50-85%)
- Postpartum depression (10-15%)

36

Postpartum Blues

- Onset 3-5 days after delivery
- Sx: weepiness, sadness, fatigue, irritability
- Tx: partner, community support
- Should resolve in 10 days. If not consider Peripartum depression

37

Postpartum Depression

- Usually develops slowly over first 3 months
- Sx- MDD sx
- Often unable to sleep
- Often see anxiety
- Up to 50% will have intrusive obsessional ruminations/images usually focused on baby. Often violent in nature but egodystonic and no problem with reality testing.

38

Postpartum Depression

- Studies vary, but the prevalence of postpartum depression is roughly 15-20%
- Distinctly different from "baby blues"
  - Mild symptoms that peak between 2-5 days post delivery and do not meet criteria for a MDE and are not severe enough to impair function
- Exact pathophysiology is not known, but suspected to be a combination of:
  - Rapid decline of hormone levels post delivery
  - Genetic factors
  - Social factors

Stewart DE, Vigod S. Postpartum Depression. N Engl J Med (2016);375;22:2177-2186.
Zhao XH, Zhang ZH. Risk factors for postpartum depression: An evidence-based systemic review of systematic reviews and meta-analyses. Asian Journal of Psychiatry 53 (2020) 102353.
Pinheiro, E. et. al. Sertraline and breastfeeding: review and meta-analysis. Arch Womens Ment Health (2015) 18:139-146.

39

Postpartum Depression

- Risk factors:
  - Hx of depression***
    - Women with untreated depression during pregnancy have a 7 times greater likelihood of developing postpartum depression
  - AND...

Violence and Abuse	Low birthweight infant	Immigration status
Gestational diabetes	Vit D deficiency	Obesity
Sleep disruption	Lack of social supports	Multiple births
Postpartum anemia	Negative birth experience	

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40

Postpartum Depression

- Preventative/Protective Factors:
  - **Treatment of peripartum depression**
  - In-home supportive care programs
  - Skin-to-skin contact and care
  - Healthy diet
  - Adequate sleep*
  - Adequate exercise*

  *- Limited data for outcomes

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Zhao XH, Zhang ZH. Risk factors for postpartum depression: An evidence-based systemic review of systematic reviews and meta-analyses. Asian Journal of Psychiatry 53 (2020) 102353.

41

Postpartum Depression

- Treatment:
  - Mild to moderate symptoms:
    - Psychotherapy often recommended as the treatment of choice
    - SSRIs are considered first line medication-based treatments
  - Severe symptoms:
    - Medication based treatment is encouraged
    - Consultation with psychiatric care if possible

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42

New medications for postpartum depression

- Brexanolone
  - Neuroactive steroid
  - Approved in 2019 for IV treatment only- 60 hours continuous infusion- rarely used
- Zuranolone
  - Neuroactive steroid
  - (FDA) has approved as the first oral agent indicated for postpartum depression- not yet available but soon
  - Dose- 50 mg/day with a fatty meal (to facilitate absorption) for 14 days, and can be used as monotherapy or in combination with other oral antidepressants

43

Insomnia in Perinatal Women

- Address treatable causes
- Behavioral therapies:
  - Sleep hygiene and stimulus control
  - Relaxation
  - Sleep restriction therapy
  - Cognitive therapy
  - Cognitive behavioral therapy for insomnia (CBT-I)
    - Free App – CBTi-Coach
- Medications considered only in severe presentations

44

Psychotropics and Breastfeeding

- Most antidepressants are transmitted in breastmilk at levels that are 10% or lower than the maternal dose
  - This is 5-10 X lower than gestational exposure
- Sertraline has substantial data demonstrating that it has some of the lowest transmission rates (often undetectable in milk)
  - Likely due to the high level of protein binding
- The impact of low dose SSRIs in breastmilk on newborns has limited data
  - Case reports are conflicting, though most common findings are irritability, restlessness, and/or colic

Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep (2016) 18:32.
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45

Psychotropics and Breastfeeding

- TCA use is generally discouraged while breastfeeding due to cardiac side effects
- Cases of newborn seizures in mothers who were breastfeeding while taking bupropion have been reported
- **Expert consensus recommends that individual decisions be made based on relative risk ratios, but SSRI use is generally considered to be safe while breastfeeding and that the risks of discontinuation are more concerning**

Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep (2016) 18:32.
Stewart DE, Vigod S. Postpartum Depression. N Engl J Med (2016);375;22:2177-2186.
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46

Psychotropics and Breastfeeding

- Benzodiazepines are also transmitted in breastmilk
  - Effective doses are low, but can lead to infant sedation
    - Occurs in < 2% of cases
    - Case reports of
      - Apnea
      - Irritability
      - Poor weight gain
- Lithium passes into breastmilk in substantial doses
  - Breastfeeding on lithium should only be attempted with close, expert consultation and support

Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep (2016) 18:32.
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47

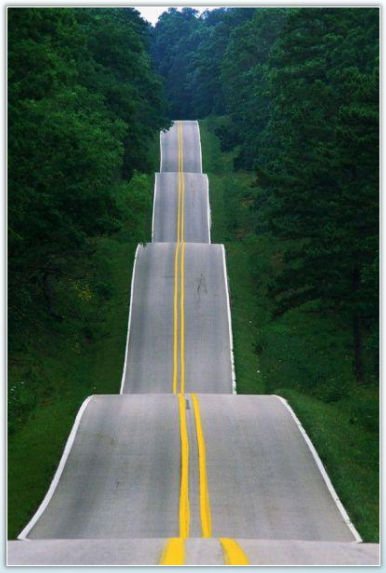
Resources

- Center for Women's Mental Health at MGH
  - https://womensmentalhealth.org/
  - This is my go-to resource for thoughtful commentary on new studies as well as great provider and patient resources to make informed decisions about mental health treatment, especially during pregnancy and breastfeeding.
- LactMed: A TOXNET DATABASE
  - https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
  - This database allows you to look up any medication and get thoughtful guidance about the use in breastfeeding mother.
- MCPAP For Moms
  - https://www.mcpapformoms.org/Toolkits/Toolkit.aspx
  - This is a great toolkit with information and decision aids to support assessing and treating perinatal depression.

48

A Little Further Down the Road...

Perimenopause and Menopause



49

Depression in Women

- Overall, woman experience depression roughly twice as frequently as men
  - This increased is generally confined to reproductive years
- The perimenopausal period is one of particularly vulnerable time with 2-5X ⇧ risk for depression
- Increased risk is predominantly seen in women with a history of MDD

Bromberger JT, Epperson, CN. Depression During and After the Perimenopause. Obstet Gynecol Clin N Am. 2018. 45:663-678.
Maki PM et. al. Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations. J of Women's Health. 2019. 28;2:117-134.

50

Can We Articulate Depression Risk in Terms of Hormonal Changes?

- **… Not really**
- Studies vary in their association of specific sex hormones with specific depression outcomes throughout the menopausal transition
  - This is complicated by the complex relationship between sex hormones, neurotransmitters, and dx
- There appear to be more consistent associations with overall change in estradiol levels rather than absolute levels
  - More about the change and lack of stability than anything else

Bromberger JT, Epperson, CN. Depression During and After the Perimenopause. Obstet Gynecol Clin N Am. 2018. 45:663-678.
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51

Menopause and Mood Disorders: Risk Factors

- Lower income
- Lower education
- Younger age
- Unpartnered
- Poor social supports
- Childhood and lifetime adversity
- Smoking
- Physical inactivity
- Sleep disturbance
- Vasomotor symptoms
- h/o depression
- h/o PMS
- Anxiety

Maki PM et. al. Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations. J of Women's Health. 2019. 28;2:117-134.

52

Treatments During Perimenopause

- Antidepressants
- Psychotherapy
- Exercise
- Estrogen

53

Which Antidepressant?

Consider...

- Prior antidepressant trials and responses
- Adverse side effects
- Safety (drug-drug interactions)
- SSRIs and SNRIs at typical doses
- Added benefit of improving menopause-related sx such as hot flashes and pain

54

Does Estrogen Treat Depression?

- Several small, double blinded studies have demonstrated estrogen therapy to be effective in improving depressive symptom rating scales in perimenopause

Bromberger JT, Epperson, CN. Depression During and After the Perimenopause. Obstet Gynecol Clin N Am. 2018. 45:663-678.
Maki PM et. al. Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations. J of Women's Health. 2019. 28;2:117-134.

55

Does Estrogen Treat Depression?

- Data indicates estrogen may be an augmentation agent for antidepressant treatment in midlife and older women but should be considered with caution
- Estrogen monotherapy is ineffective in treating symptoms of depression in **postmenopausal** women
- Estrogen is NOT an FDA approved treatment for depression

Bromberger JT, Epperson, CN. Depression During and After the Perimenopause. Obstet Gynecol Clin N Am. 2018. 45:663-678.
Maki PM et. al. Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations. J of Women's Health. 2019. 28;2:117-134.

56

What about estradiol + micronized progesterone?

- RTC Twelve-month study of women given transdermal estradiol + intermittent micronized progesterone were more effective than placebo in preventing the development of clinically significant depressive symptoms among **initially euthymic** perimenopausal and early postmenopausal women.

Gordon et al. Efficacy of Transdermal Estradiol and Micronized Progesterone in the Prevention of Depressive Symptoms in the Menopause Transition. Jama Psychiatry 2018:75(2):149-157

57

Estrogen and dementia risk

- Effect is complex and depends on the timing and type of therapy; mid-life estrogen use around the time of menopause may be linked to a reduced risk of dementia, while late-life estrogen use has been associated with an increased risk.
- Addition of progestins to estrogen therapy may blunt any potential protective effects.
- Bottom line- need large clinical trials to establish a definitive link

Noor Ali et al The Role of Estrogen Therapy as a Protective Factor for Alzheimer's Disease and Dementia in Postmenopausal Women: A Comprehensive Review of the Literature. Cureus. 2023 Aug 6;15(8):e43053.

58

Sleep disturbance and menopause

59

Etiology

- Sleep disturbance is often attributed to nocturnal hot flashes AND
- Recent study suggests that a sizable portion of menopausal women may have a primary sleep disorder

60

Treatment: nonpharmacologic

- Studies have evaluated the impact of group CBT, self-help CBT on peri- and post-menopausal women with problematic vasomotor symptoms (10 or more hot flashes or night sweats per week)
- Women engaging in various forms of CBT reported significantly reduced hot flash and night sweat symptom ratings compared to women in the no treatment control groups. There were also improvements in mood, sleep and quality of life.

Ayers B, et al Effectiveness of group and self-help cognitive behaviour therapy to reduce problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. Menopause. 2012; 19(7):749-759
Stefanopoulou E, et al. Telephone-guided Self-Help Cognitive Behavioural Therapy for menopausal symptoms. Maturitas. 2014 Jan;77(1):73-7.

61

Pharmacologic treatments

- **Estrogen replacement therapy:** Can improve sleep however many women cannot or do not want to use hormone therapy.
- **Sedative-hypnotic agents:** Zolpidem (Ambien) and zaleplon (Sonata), are commonly used in this population. Can be effective but not appropriate for long-term use.
- **Benzodiazepines:** Frequently used to treat insomnia. Not be an ideal long-term option given concerns regarding their use in older patients.

62

Pharmacologic treatments

- **Serotonin reuptake inhibitors:** May improve sleep via reducing vasomotor symptoms that interfere with sleep and via treating anxiety and depressive symptoms, which also lead to sleep disruption.
- **Gabapentin (Neurontin):** May improve sleep quality and decrease vasomotor symptoms. In addition, it is well-tolerated and free of serious side effects.

63

Take Home Points

- Risk/Risk assessments in the peri and postpartum period require multifactorial consideration and open communication
- The impact of untreated or undertreated depression should not be overlooked in favor of reducing possible risks from medication-based treatment of depression
- SSRI use during breastfeeding is generally considered to be safe enough to support continued SSRI use while breastfeeding in women with significant depression and/or anxiety disorders
- The perimenopausal period is a high-risk time for depression so look for it and treat it!

64

SSRIs and Risk of Spontaneous Abortion

- Kjaersgaard et al. 2013: Population based study of pregnancies in Denmark reported 12% rate of spontaneous abortion with exposure to antidepressants
  - RR 1.14 (95% CI 1.10-1.18)
  - RR lowered to 1.0 when compared to spontaneous abortion rates in women with depression who did not take an antidepressant
- Andersen et al. 2014: Large study of pregnancies in Denmark
  - Adjusted hazard ratio of spontaneous abortion with exposure to an SSRI of 1.27 (95% CI 1.22-1.33)
  - Adjusted hazard ratio of spontaneous abortion with discontinuation of an SSRI one year prior to pregnancy of 1.24 (95% CI 1.18-1.30)

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.
Kjaersgaard MIS, Parner ET, Vestergaard M. et al. Prenatal antidepressant exposure and risk of spontaneous abortion – a population-based study. PLoS One 2013;8:e72095.
Andersen JT, Andersen NL, Howitz H, et al. Exposure to selective serotonin reuptake inhibitors in early pregnancy and the risk of miscarriage. Obstet Gynecol 2014; 124:655-61.

65

SSRIs and Birth Outcomes

- Numerous studies have examined outcomes related to preterm birth and low birth weight
  - 2013 systemic review and metanalysis found:
    - Pooled OR 1.55 (95% 1.38-1.74) of preterm birth in mothers taking antidepressants
      - Averaged 3 days shorter gestational age
  - Same analysis found a mean birthweight difference of -74 grams in newborns exposed to SSRIs during gestation (95% CI -117 to -31)
    - ~2% birthweight of a 3.5 kg newborn

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.
Ross LE, Grigoriadis S. Mamisashvili L, et. al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systemic review and meta-analysis. JAMA Psychiatry 2013;70:436-43.

66

Congenital Malformations

- Studies have varied somewhat in findings
  - Huybrechts KF et. al. 2014 NEJM found no substantial increase in the risk of cardiac malformation with first-trimester exposure to antidepressants
  - Other, contemporary studies have found an increased risk of malformations with SSRIs, particularly paroxetine, though the clinical significance of findings has been inconsistent
  - Reports of increased risk of malformations usually report OR of 1.2 to 2.0

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.
Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep (2016) 18:32.

67

Persistent Pulmonary Hypertension of the Newborn (PPHN)

- PPHN occurs in 1.9 infants per 1000 live births
  - Range of complications and outcomes, but mortality can be 10-20%
- Studies have been somewhat inconclusive in that some demonstrate and association with SSRI use in late pregnancy and others do not
  - Caused the FDA to revise their 2006 warning in 2011
- Studies that do show an association demonstrate an absolute risk of 2.9-3.5/1000 with SSRI use in late pregnancy

T Pearlstein. Depression During Pregnancy. Best Practice & Research Clinical Obstetrics and Gynecology 29 (2015) 754-764.
Becker M, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep (2016) 18:32.

68