MATERNAL MENTAL HEALTH: ADDRESSING PERI–AND POSTPARTUM DEPRESSION

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Learning Objectives

• Implement evidence-based strategies to manage depression during pregnancy

• Counsel patients about the risks vs. benefits of medication treatment during pregnancy and postpartum

• Compare the safety profiles of treatment options for depression during the postpartum period
Depression During Pregnancy
Epidemiology of Mood Disorders During Pregnancy

- **Prevalence rates**
  - First trimester 7.4%
  - Second trimester 12.8%
  - Third trimester 12.0%

- **Bipolar disorder**
  - 5.1% of women at an obstetric clinic
  - 12% of women referred to a women's mental health program for psychiatric assessment during pregnancy

- **Prevalence of anxiety disorders and obsessive compulsive disorder (OCD) is also high during pregnancy**

Risks of Untreated Depression in Pregnancy

• Effect on child development
  • Higher impulsivity, maladaptive social interactions, and cognitive, behavioral, and emotional difficulties

• Maternal
  • Pregnancy complications such as eclampsia, postpartum depression, safety concerns, hospitalization
  • Engagement in high-risk behaviors such as smoking, ETOH use, illicit drug use, and poor nutrition
  • Increased risk of suicide

The American College of Obstetricians and Gynecologists (ACOG) recommends: women should be screened for depression and anxiety symptoms at least once during the perinatal period.

Clinical Management During Pregnancy

<table>
<thead>
<tr>
<th>Women Currently Taking Medication</th>
<th>Women Not Currently Taking Medication</th>
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<tbody>
<tr>
<td>• Psychiatically stable women who prefer to stay on medication may be able to do so after consultation to discuss risks and benefit</td>
<td>• Psychotherapy may be beneficial in women who prefer to avoid ADs</td>
</tr>
<tr>
<td>• Women who would like to discontinue medication may attempt tapering depending on current status and psychiatric history</td>
<td>• For women who prefer taking medication, risks and benefits of treatment choices should be evaluated and discussed, including factors such as stage of gestation, symptoms, prior history of depression, and other conditions and circumstances (e.g., a smoker, difficulty gaining weight)</td>
</tr>
<tr>
<td>• Women with current symptoms despite their medication or recurrent depression may benefit from psychotherapy to replace or augment medication</td>
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<tr>
<td>• Women with severe depression (with suicide attempts, functional incapacitation, or weight loss—7–9 depressive symptoms. &gt; 20 on PHQ-9) should remain on medication</td>
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<tr>
<td>• If patient refuses medication, alternative treatment and monitoring should be in place, preferably before discontinuation</td>
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SSRI Use During Pregnancy

• Prevalence of SSRI use during pregnancy is 3% to 7%

• Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
  • Consistent conclusions that the *absolute* risk of malformations with SSRI exposure in pregnancy is small
  • Recent case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs

• Reproductive safety data on SSRI exceed what is known about most other medicines used in pregnancy

SSRI, selective serotonin reuptake inhibitor.


• Analysis of 949,504 pregnant women enrolled in Medicaid – 3 months prior to pregnancy to 1 month following pregnancy
• 6.8% use of SSRIs during first trimester
• No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs

Are SSRIs associated with increased risk of autism?

1) **Canadian Study**: Health administrative data sets factored in large number of potential confounders and compared exposed children with unexposed siblings
   - 35,906 singleton births: After factoring in propensity scores for confounding, **association not significant**; association also not significant when exposed children were compared with unexposed siblings

2) **Swedish Study**: Controlled for pregnancy, maternal and paternal covariates, sibling comparisons, timing of exposure
   - Offspring born to 943,776 mothers
   - First trimester exposure associated with a small increased risk of preterm birth, but no increased risk of small for gestational age, autism spectrum disorder, or ADHD

ADHD: attention-deficit/hyperactivity disorder.
Increased Risk of Autism With Untreated or SSRI-Treated Psychiatric Disorder During Pregnancy

Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension

- Of 3.8 million pregnancies
  - 128,950 women (3.4%) filled at least one prescription for antidepressants during last 90 days of pregnancy
    - 2.7% used an SSRI
    - 0.7% used a non-SSRI
  - 7630 infants (20.8 per 10,000 births) not exposed to antidepressants were diagnosed with PPHN
  - 322 infants (31.5 per 10,000 births) exposed to SSRIs
  - 78 infants (29.1 per 10,000 births) exposed to non-SSRIs

- **Absolute Risks:**
  - With SSRI: 31.5/10,000 = 0.3%
  - No antidepressant: 20.8/10,000 = 0.2%

- Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment

Other Interventions

• rTMS
  - Two open studies with the largest samples reported
  - Response: 41.4% to 70%, Remission: 20.7% to 30%, Partial Response: 34.5%

• Exercise
  - Effect size for physical activity interventions during pregnancy and the postpartum period was 0.41 (95% CI, 0.28-0.54)

• Others
  - Folate, bright light therapy, massage and acupuncture have been studied but lack of rigorous studies

Postpartum Depression
# Postpartum Depression vs. Baby Blues

<table>
<thead>
<tr>
<th></th>
<th>Baby blues</th>
<th>Postpartum depression</th>
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</thead>
<tbody>
<tr>
<td><strong>PREVALENCE</strong></td>
<td>75%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>DURATION</strong></td>
<td>Resolves by day 10 postpartum</td>
<td>Minimum 2 weeks</td>
</tr>
<tr>
<td><strong>SYMPTOMS</strong></td>
<td>Mood lability, Tearfulness, Irritability, Confusion, Fatigue</td>
<td>Diagnostic criteria for MDD</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Support, reassurance, adequate sleep</td>
<td>Pharmacological and non-pharmacological treatments</td>
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</table>
GABA$_A$ Receptor Modulation of the HPA Axis

- Corticotropin (ACTH)
- Glucocorticoid receptor
- Cortisol
- Corticotropin-releasing factor (CRF)
- Placental corticotropin-releasing factor (pCRF)
- Allopregnanolone
- GABA
- GABA$_A$R
- Blood-brain barrier

Hippocampus
Hypothalamus
Pituitary
Adrenal

Allopregnanolone and estrogen levels normal
HPA Axis in Pregnant Females

1. Corticotropin (ACTH)
2. Glucocorticoid receptor
3. Cortisol
4. Corticotropin-releasing factor (CRF)
5. Placental corticotropin-releasing factor (pCRF)
6. Allopregnanolone
7. GABA
8. GABA<sub>A</sub>R

Allopregnanolone and estrogen levels HIGH

1. Acute stressor

2. Allopregnanolone and estrogen levels LOW

3. Blood-brain barrier

4. GABA

GABA<sub>A</sub>R

Postpartum Depression (PPD)

- Postpartum depression is the most common complication of childbirth
  - 10–20% of new mothers
- 40–80% of postpartum depression cases are considered moderate-severe
- 25–40% with a prior history of depression will experience PPD
- Onset
  - During the postpartum period (40.1%)
    - Onset during first 4 months postpartum in as many as 94% of cases
  - During pregnancy (22–33%)
  - May be a recurrence of unipolar or bipolar depression episode occurring during or prior to pregnancy
- 40% of women with PPD will have a relapse during subsequent perinatal periods

Untreated Postpartum Depression

• Due to:
  • Reluctance to seek help because of guilt over feeling depressed during a period society views as joyful
  • Stigma
  • Reluctance to utilize medication during lactation
  • Lack of screening
  • Poor coordination of care

• Risks of untreated PPD
  • Increased maternal morbidity and mortality
  • Epigenetic changes to infant glucocorticoid receptor genes (altered HPA axis reactivity)
  • Impaired child emotional and cognitive development
  • Infant mortality

Risk Factors for Postpartum Depression

- Anxiety and depression during pregnancy
- Previous episode of PPD
- Previous history of depression
- Heightened hypothalamic-pituitary-adrenal (HPA) axis sensitivity to hormonal changes
- Unwanted pregnancy
- Experiencing stressful life events during pregnancy or the early postpartum
- Low levels of social support

DSM-5 Criteria

- *DSM-IV* specifier: with postnatal onset
- *DSM-5* specifier: with peripartum onset
  - Onset during pregnancy or within 4 weeks postpartum

Issues
- Depression during pregnancy vs. postpartum depression
  - Different etiologies?
  - Different treatments?
- Onset
  - Argument that postpartum depression may occur anytime during first year

Screening for PPD

- The US Prevention Task Force Services and the American College of Obstetrics and Gynecologists recommend screening for depression at least once during the postpartum period.
- Clinician overall impression of maternal health detects <30% of PPD cases.
- Edinburgh Postnatal Depression Scale (EPDS)
  - 10-item Likert-style questionnaire
  - 5 minutes to complete
  - Score of 10+ deserves attention
- Postpartum Depression Screening Scale (PDSS)
  - 35-item Likert-style questionnaire
  - 5–10 minutes to complete
  - Score of 60+ deserves attention.

Antidepressants

• Prevention of PPD
  • Mixed results
  • Cochrane review concluded that antidepressants showed modest benefit in preventing peripartum depression; however, insufficient data to recommend their use
  • Antidepressant use during third trimester in euthymic women did not prevent postpartum depression
    • 10% of those taking antidepressant developed PPD vs. 13% of those not taking antidepressant

• Treating PPD
  • Cochrane review concluded that there is insufficient evidence to say whether, and for whom, antidepressant or psychosocial treatments are more effective

Efficacy and Safety of Antidepressants for PPD

• Several antidepressants (e.g., sertraline, nortriptyline, escitalopram) have shown efficacy for PPD

• Agency for Healthcare Research and Quality (AHRQ) reports insufficient data for the efficacy of antidepressants for PPD but no evidence of harm to mothers or infants

*Response rate defined as score of ≤10 on HAM-D, minimum 50% decrease HAM-D score from baseline, and at least “much improved” on CGI

Postpartum Use of Antidepressants

• Before initiating an antidepressant, screen all patients diagnosed with PPD for evidence of bipolar disorder

• Antidepressants should be used with caution in antidepressant-naive women who experience their first depressive episode in the postpartum period

• Caution also needs to be exercised while using antidepressants in women who have mixed depression

• Antidepressants should be tapered if the patient develops postpartum psychosis, and treatment should be carried out with initiation/optimization of mood stabilizer or atypical antipsychotic with mood stabilizing properties
Breastfeeding and Antidepressants

Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum\(^1,2\)

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Description</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>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; reasonable to consider if used during pregnancy</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Consistent reports of low levels of exposure; relatively large amount of study</td>
</tr>
<tr>
<td>Citalopram, escitalopram</td>
<td>Less systematic study of mom-baby pairs compared with sertraline and paroxetine; observed low levels of exposure to infant via breastfeeding</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Consistent reports of low levels of exposure; relatively large amount of study; use limited by commonly experienced withdrawal symptoms; may be more sedating than other SSRIs</td>
</tr>
<tr>
<td>Bupropion</td>
<td>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</td>
</tr>
<tr>
<td>Venlafaxine, desmethyl-venlafaxine</td>
<td>Higher levels of desmethylvenlafaxine found in breastmilk than venlafaxine; no adverse events reported</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Considered reasonable for breastfeeding if use is clinically warranted; few adverse effects in babies, and generally low levels of exposure reported</td>
</tr>
<tr>
<td>Mirtazapine, nefazodone, MAOIs, duloxetine</td>
<td>Systematic human testing lacking in the context of breastfeeding</td>
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Presentations of PPD in Which Antidepressants Should Be Avoided or Used Cautiously

- Major depressive disorder with mixed features
- Major depressive episode with first onset in the postpartum period
- Major depressive episode with onset in early postpartum
- History of bipolar disorder in first-degree relative
- Atypical features
  - Hypersomnia, leaved paralysis, or increased appetite

Mood Stabilizers and Breastfeeding

• Considerable amount of lithium and lamotrigine are excreted into breast milk

• Paucity of data on valproate and oxcarbazepine; however, the infant-maternal ratio of serum drug concentration seems to be lower in valproate exposure compared to other mood stabilizers

• Incidence of adverse events in infants exposed to mood stabilizers is reportedly very low

• Mood stabilizers can be prescribed to most lactating women without any adverse events in infants

• Low prevalence rate of laboratory abnormalities, including hepatic, kidney, and thyroid functions in the infants

Lithium

- Breastfeeding during lithium treatment remains controversial
- Contraindicated at one time by the American Academy of Pediatrics
- Revised to classification “Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution”
- Toxicity reported in cases with infant serum levels at 0.1–0.5x the maternal level
  - Recommend checking infant lithium levels at 4–5 weeks postpartum and every 8 weeks ongoing during breastfeeding

Antipsychotics

• Atypical antipsychotics with mood-stabilizing properties are recommended first-line for depression with mixed features (including PPD?)
  • Lurasidone
  • Quetiapine
  • Asenapine
  • Olanzapine
  • Ziprasidone

• Antipsychotics may have a better risk-benefit ratio compared to some mood stabilizers

• Antipsychotic levels in breastmilk have generally been found to be low

Brexanolone

- Aqueous formulation of the neuroactive steroid allopregnanolone
  - Positive allosteric modulator of GABA_A receptors
- Administered over 60 hours via single, continuous IV infusion
  - 60 ug/kg or 90 ug/kg per hour vs. placebo
- Dramatic reductions in depressive symptoms (HAM-D and MADRS) within 24 hours for many patients
- Response sustained for 30 days
- Common side effects (occurring in ~30% of patients)
  - Include:
    - Somnolence
    - Dizziness
    - Sedation
  - Consistent with GABAergic actions

SAGE-217 (Zuranolone) for Severe PPD (ROBIN study)

- N=151, Ages 18-45
- Results:
  - Decrease in HAM-D
  - Day 3: zuranolone -12.5 vs placebo -9.8 (p=0.0255)
  - Day 14: (Primary endpoint) zuranolone -17.8 vs placebo -13.6 (p=0.0029)
  - Difference was maintained to the end of 4 week follow-up period
- Response: zuranolone 72% vs placebo 48%
- Remission: zuranolone 45% vs placebo 23%

- HAM-A and CGI-I were also significantly better for zuranolone
- Most common AEs: somnolence/sedation, dizziness, URI, diarrhea

Other Treatments for PPD With Limited Evidence

- ECT
- Hormonal therapy (e.g., estrogen patch)
- Bright light therapy
- rTMS
- Omega-3 fatty acids
- Folate
- SAMe
- St. John’s wort
- Exercise
- Massage
- Acupuncture

Psychotherapy for Prevention of PPD

- Subthreshold depressive symptoms or women with risk factors for PPD
- Supportive and psychological care (e.g., home visits, telephone support) was associated with a lower risk of PPD than standard care (information booklets, routine antenatal classes, and routine peripartum care by a primary care provider)
- Supportive and psychological interventions more effective when delivered postnatally than antenatally

Detecting PPD—Who’s Responsible?

- PPD offers a unique opportunity for prevention/treatment
  - Occurs within a limited/delineated timeline following a concrete event

- Pediatricians
  - Pediatric well-baby visits may be the only consistent contact with clinicians during the first year postpartum
    - 70% of pediatricians never screen for PPD
    - The American Academy of Pediatrics recommends screening for PPD at 1-, 2-, and 4-month well-baby visits

- OB/GYNs
  - Limited contact with new mothers after childbirth
  - 30% never assess for maternal depression

Summary

• When it comes to perinatal depression, women, children, and families are impacted

• Effective, safe, accessible, and acceptable treatments are needed

• Treatment considerations involve risks of medications vs. risks of the untreated disorder

• Drastic hormonal changes occurring postpartum, in interaction with GABA<sub>A</sub> receptors and subsequent modulation of the HPA axis, are thought to underlie postpartum depression

• The novel allopregnanolone formulation, brexanolone, may offer a more effective and faster-acting treatment for PPD