DIAGNOSIS AND TREATMENT OF POSTPARTUM DEPRESSION
Learning Objectives

• Improve the recognition of postpartum depression
• Optimize treatment for patients with postpartum depression
Epidemiology of Postpartum Depression (PPD)

- Worldwide incidence and prevalence of PPD is approximately 12% and 17%, respectively.
- Prevalence is 6.9–12.9% in high-income countries and >20% in low-income countries.
  - Highest prevalence in Middle Eastern countries (26%).
  - Lowest prevalence in European countries (8%).

Suicide in the Postpartum

• Suicide deaths and attempts are lower during postpartum than in the general population of women

HOWEVER

• Suicide is the second leading cause of mortality in postpartum women
• Postpartum suicide is characterized by violent and lethal means

PPD in Adolescence

• Higher prevalence of PPD among Adolescents (~25%) than adults (~17%)

• Suicidal behavior in postpartum adolescents is higher than the general population of adolescent girls and women

• Adolescent mothers face more psychosocial challenges (e.g., lower social support and socioeconomic status) that increase risk for PPD

“Major Depressive Disorder, With Peripartum Onset” DSM-5 Diagnostic Criteria

- Diagnostic criteria are the same as major depression
- **Peripartum specifier** stipulates symptom onset within 4 weeks of delivery
- In clinical practice and research, symptom onset within 12 months of delivery may be considered PPD

### Major Depression Diagnostic Criteria

*Five or more symptoms present ≥2 weeks; change from previous functioning; causing clinically significant distress*

- Depressed mood
- Anhedonia
- Sleep and appetite disturbance
- Impaired concentration
- Psychomotor disturbance
- Fatigue
- Feelings of guilt or worthlessness
- Suicidal thoughts

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Additional Symptoms Common to PPD

- Irritability
- Mood lability
- Anxiety
- Feeling overwhelmed
- Thoughts of harming child
- Obsessional worries or preoccupations with baby

PPD Detection

- Ask all postpartum women about feelings in past month:
  - Feeling down, depressed, or hopeless?
  - Bothered by little interest or pleasure in doing things?
- If positive answer to either question:
  - Administer Edinburgh Postnatal Depression Scale (EPDS) or other screening questionnaire
- Score indicating PPD in a screening tool
- Clinical interview to confirm diagnosis

The American College of Obstetrics and Gynecology (ACOG) recommends all mothers be screened for PPD within 3 weeks of giving birth.

Edinburgh Postnatal Depression Scale (EPDS)

- Easy to administer, 10-item questionnaire about feelings in the past 7 days
- Items scored 0–3 depending on severity of symptoms
- Total score is sum of all 10 items (max score 30)
- A score ≥10 or a positive response to item 10 (i.e., self-harm ideation) indicate possible depression and require clinical evaluation

Depressive symptoms secondary to untreated medical conditions (e.g., thyroid dysfunction, anemia) or alcohol or other substance abuse must also be ruled out.

### Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing Features From PPD</th>
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</table>
| Postpartum blues                   | • Less severe and persistent symptoms  
• Onset of symptoms always during postpartum  
• Typically no severe obsessional preoccupations or suicidality |
| Adjustment disorders               | • Fewer and less severe symptoms  
• Improvement after mitigating stressors                                                      |
| Posttraumatic stress disorder (PTSD) | • Remote or recent traumatic events associated with nightmares, flashbacks, or other symptoms of PTSD |
| Bipolar disorder                   | • Manic or hypomanic symptoms                                                                  |
| Postpartum psychosis (PPP)         | • Delusions, grandiosity, hallucinations, confusion, bizarre behavior, or disorganized thoughts, accompanied by depression or mania |

The strongest risk factor is a history of mood or anxiety disorder, especially if symptomatic during pregnancy.

Howard LM et al. Lancet 2014;384(9956):1775-88;
Wisner KL et al. JAMA Psychiatry 2013;70(5):490-8;
Postpartum Anxiety Is More Common Than You Think

• An estimated 8.5% of postpartum women are diagnosed with one or more anxiety disorders

• Approximately two-thirds of women with PPD have a comorbid anxiety disorder or symptoms

• Women with postpartum depression and anxiety diagnoses display poorer quality of life and their illness is slower to remit than women with postpartum depression only

• DSM-5 specifies no diagnosis of postpartum anxiety disorder and no standardized diagnostic criteria exist

Course of PPD Illness

• 33% of women experience depression during pregnancy (i.e., antepartum depression)

• With treatment, most cases resolve within a few months

HOWEVER

• 24% are depressed 1 year after giving birth despite receiving treatment

• 13% are depressed 2 years after giving birth despite receiving treatment

• 40% will relapse during subsequent pregnancy or unrelated to pregnancy

PPD Outcomes

Mother

- ↓ Physical health
- ↓ Psychological health
- ↓ Quality of life
- ↑ Relationship problems
- ↑ Risky behavior

Infant

- ↓ Quality of sleep
- ↓ Cognitive development
- ↓ Language development
- ↑ Health concerns
- ↑ Behavioral problems

Mother-Infant Interactions

- ↓ Bonding and attachment
- ↓ Maternal care
- ↑ Breastfeeding problems

Reduction in Rate of Subsequent Live Births Following Postpartum Psychiatric Illness

• Women with postpartum psychiatric illness after their first birth demonstrate a decline in subsequent live births

• The reduction in subsequent live births is
  • 33% for women with any postpartum psychiatric illness;
  • 39% for women with postpartum depression; and
  • 47% for women with any postpartum psychiatric illness with hospitalization (indicating greater severity)

• In women with postpartum psychiatric illness whose first child died, there is no reduction in subsequent births, suggesting that the reduction in subsequent live births in this population is at least, in part, voluntary

Pathophysiological Mechanisms Implicated in PPD

**Neurotransmitter Alterations**
- GABA, glutamate, serotonin, dopamine

**Neuroendocrine Changes**
- Allopregnanolone, progesterone, estrogen, oxytocin, prolactin, cortisol, ACTH, CRH

**Neuroinflammation**
- IL-6, IL-1β, IL-8, TNF-α, IFN-γ

**Neurocircuit Dysfunction**
- Amygdala, prefrontal cortex, cingulate cortex, insula

**Genetics/Epigenetics**
- ESR1, 5-HTT, MOAO, COMT, TPH2, OXT/OXTR, HMNC1, HPA pathways


5-HTT: serotonin transporter
ACTH: adrenocorticotropic hormone
COMT: catechol-O-methyltransferase
CRH: corticotropin releasing hormone
ESR1: estrogen receptor alpha gene
GABA: gamma aminobutyric acid
HMNC1: Hemicentin 1 gene
HPA: hypothalamic-pituitary-adrenal
IFN: interferon
IL: interleukin
MOAO: monoamine oxidase A
OXT: oxytocin
OXTR: oxytocin receptor
TNF: tumor necrosis factor
TPH2: tryptophan hydroxylase 2
Evidence-Based Treatment Recommendations

All PPD
- Self-care
- Sleep protection
- Exercise
- Psychosocial support strategies
- Investigate and manage social stressors, medical and psychiatric comorbidities

Moderate PPD
- Psychological treatments, including cognitive behavioral therapy and interpersonal therapy
- Add selective serotonin reuptake inhibitor (SSRI) if insufficient response
- Brexanolone

Severe PPD
- SSRI alone or with psychological intervention
- Consider antidepressant switch and augmentation strategies if no response to SSRI alone
- Brexanolone
- Consider electroconvulsive therapy with severe suicidality or treatment resistance

## Psychological Interventions Reduce Depression Symptoms in Women With PPD

Data from meta-analysis of 10 studies with randomized controlled design (N=1,324) examining change in depressive symptoms following psychological interventions for PPD in primary care.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Change in Depression Symptoms Immediately Post-intervention, SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive behavioral therapy</td>
<td>-0.36 (-0.52 to -0.21) *</td>
</tr>
<tr>
<td>Interpersonal therapy</td>
<td>-0.93 (-1.27 to -0.59) *</td>
</tr>
<tr>
<td>Counseling</td>
<td>-0.29 (-0.53 to -0.05) *</td>
</tr>
<tr>
<td>Other psychological interventions</td>
<td>-0.23 (-0.46 to 0.01) #</td>
</tr>
<tr>
<td>Total</td>
<td>-0.38 (-0.49 to -0.27) *</td>
</tr>
</tbody>
</table>

SMD=standardized mean difference; CI=confidence interval. *p<0.05, #p=0.06 test for overall effect.

Psychological interventions also significantly reduced depressive symptoms 6 months post-intervention (SMD = -0.21) and were significantly better than control conditions for reducing symptoms below threshold (odds ratio [OR] = 2.24).

Efficacy of SSRIs for the Treatment of PPD

Meta-analysis of 3 randomized controlled trials with parallel group design (N=146, PPD onset up to 6 months after giving birth) comparing effects of SSRIs (sertraline [2 studies] and paroxetine [1 study]) and placebo.

Sertraline

• Sertraline is the SSRI with the most evidence in the treatment of PPD

• Effects of sertraline treatment may be more pronounced in women who have an onset of PPD within 4 weeks of childbirth

• There is evidence of sertraline efficacy in combination with CBT for treating PPD

Brexanolone

- The only FDA-approved (2019) treatment for postpartum depression
- Neuroactive steroid chemically similar to allopregnanolone, a positive allosteric modulator of GABA<sub>A</sub> receptor
- Administered intravenously over 60 hours in a single dose
- Most common adverse events:
  - Sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush
  - Use with antidepressants may increase sedation
- Ongoing clinical trial to test safety, tolerability, and pharmacokinetics in adolescents with PPD (NCT03665038)

Efficacy of Brexanolone for the Treatment of PPD

Meta-analysis of randomized control trials (3 studies; n=267) comparing brexanolone vs. placebo effects on depression response (≥50% reduction of Hamilton Depression Rating Scale [HAMD] total score) and remission (HAMD total score ≤7) in women with moderate-to-severe PPD.


*p≤0.02 compared to placebo
Brexanolone: Barriers to Access

- Very expensive: ~$34,000 per treatment alone and additional indirect costs for infusion, continuous monitoring, health care providers, and required hospital stay

- Available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)

- No published data to support its use for mild PPD

- Concerns remain about sustained efficacy

- Interruption in normal mother-child interactions due to patients being isolated from or supervised in the presence of their children during infusions

- May be advantageous for patients requiring rapid response due to disease severity

Burval J, Reed K. Nursing 2020;50(5):48-53;
Efficacy and Safety of Zuranolone for Severe PPD (ROBIN Study)

Results from a phase 3, randomized, double-blind study of women with severe PPD (N=151) treated with daily oral zuranolone (30 mg) or placebo for 2 weeks

• Decrease in Hamilton Depression Rating Scale (HAMD-17)
  • 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 the 4-week follow-up period (p=0.0027)
  • Response at Day 14: zuranolone 72% vs placebo 48% (p=0.0050)
  • Remission at Day 14: zuranolone 45% vs placebo 23% (p=0.0122)

• The most common adverse events (≥ 5%) were somnolence/sedation, headache, dizziness, upper respiratory infections, and diarrhea

Other Treatments With Limited Research Evidence of Efficacy in PPD

- Venlafaxine
- Desvenlafaxine
- Bupropion
- Nefazodone
- Nortriptyline
- Transdermal estradiol patches

- Repetitive transcranial magnetic stimulation
- Transcranial direct-current stimulation
- Omega-3 fatty acids
- Vitamin D
- Yoga

Frieder A et al. CNS Drugs 2019;33(3):265-82;
Considerations for Breastfeeding: Antidepressants

- Infant exposure through lactation should be considered when recommending pharmacological treatment
- Most antidepressants are not contraindicated during breastfeeding
- No direct evidence that antidepressants are unsafe in pregnancy

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Relative Infant Dose, %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>2</td>
</tr>
<tr>
<td>Citalopram</td>
<td>3 – 10</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>5.5 – 8.1</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>&lt; 12</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.5 – 3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.5 – 3</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0.5 – 3</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>6 – 9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative infant dose ≤10% is associated with decreased risk to infant.
Considerations for Breastfeeding: Brexanolone

- Relative infant dose in breast milk 36 hours after brexanolone infusion is 1-2%.
- Oral bioavailability is low (<5%).
- No data on effects of milk production or effects on breastfed infants.

Considerations for Breastfeeding: Pump and Dump

• Infant daily dose in breastfeeding with SSRI use can be reduced by “pump and dump” at 8 to 9 hours after maternal medication

• Drug concentrations tend to be higher in hindmilk because of its lipophilic nature

PPD Prevention in Pregnant and Postpartum Women

• Counseling services (i.e., cognitive behavioral therapy and interpersonal therapy) are recommended for high-risk women

[Diagram showing high-risk factors]

- History of depression
- Current depressive symptoms
- Low income
- Young or single parenthood

Summary

• PPD has a prevalence of 17% and is the second leading cause of death among postpartum women

• Screening for PPD should occur regularly beginning within 3 weeks of giving birth

• Severity of PPD symptoms and patient preferences should guide treatment selection
  - **Mild**: psychosocial support strategies
  - **Moderate**: CBT/IPT alone or with SSRI; brexanolone
  - **Severe**: SSRI alone or with CBT/IPT; brexanolone; ECT (with severe suicidality, treatment resistance)
Monica is a first-time, single mother who gave birth to a healthy son 4 weeks prior. She lives alone with her child and has been receiving help from her mother a few times a week since her son was born. During a postpartum visit she reports feeling overwhelmed, fatigued and irritable since the birth of her son. She is having trouble concentrating and reports feeling like a “terrible mother.” She denies suicidal thoughts or behavior. Screening with the Edinburgh Postnatal Depression Scale results in a score of 11.

Based on this information, what intervention would be most appropriate for Monica at this time?

A. Psychosocial support strategies
B. Cognitive behavioral therapy
C. Treatment with sertraline
D. Treatment with brexanolone
A 31-year-old woman is diagnosed with severe postpartum depression 3 weeks after giving birth. The patient is hesitant about starting pharmacological treatment because she would like to continue breastfeeding her child.

Which statement is the most accurate regarding pharmacological treatments for postpartum depression?

A. Serotonin-norepinephrine reuptake inhibitors have the best lactation safety profile
B. Brexanolone has minimal effects on breast milk production
C. Most antidepressants are not contraindicated during breastfeeding