Postpartum Depression: What Every Clinician Should Know
Women’s Reproductive Lifecycle
Learning Objectives

• Overview of postpartum depression (PPD)
  – Review common psychiatric disorders in postpartum period
  – Review risk factors and recent theories around underlying biology
  – Discuss several examples of vulnerable groups that crosses risk factors

• Discuss identification and treatment of PPD
  – Review screening and identification
  – Review psychopharmacologic treatment
  – Review non-pharmacologic treatments
  – Discuss novel, investigational treatments and studies
**Postpartum Depression is Common, Morbid, and Often Missed**

<table>
<thead>
<tr>
<th>Common</th>
<th>Morbid</th>
<th>Missed</th>
<th>Heterogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20% Prevalence</td>
<td>Devastating Consequences</td>
<td>Inconsistent Use of Practice Guidelines &amp; Routine Screening</td>
<td>Timing of Onset</td>
</tr>
<tr>
<td>Most common unrecognized complication of perinatal period</td>
<td>Low Maternal Weight Gain Pre-term Birth</td>
<td>Symptoms often different from “Classic DSM Depression”</td>
<td>Symptom Presentation</td>
</tr>
<tr>
<td></td>
<td>Impaired Attachment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase Risk: Suicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infanticide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Postpartum Blues - Not a Disorder

- The “Baby Blues”
- 50% to 85% of women experience postpartum blues
- Crying easily, emotional lability, irritability, sleep and appetite disturbances
- Onset 2-3 days after birth, last less than 2 weeks
- Due to abrupt hormone withdrawal
  - Progesterone (and allopregnanolone) levels are higher the day before delivery and decrease after delivery corresponding to a peak in blues score
- Is postpartum blues a precursor to postpartum depression?

Harris, 1994; Nappi, 2001; Miller for review, 2002; Henshaw, 2004; Reck, 2009; Bloch, 2003
Major Depressive Disorder

• DSM-5 has a “peripartum” qualifier—now includes in pregnancy and postpartum onset

• Either depressed mood or loss of interest or pleasure in activities for greater than 2 weeks, accompanied by:
  – Sleep disturbances
  – Appetite disturbances
  – Psychomotor agitation or retardation
  – Loss of energy
  – Decreased concentration
  – Suicidal thoughts
Postpartum Depression

• Same definition as for a Major Depressive Disorder only occurs within one month of delivery
  – Either depressed mood or loss of interest or pleasure in activities for greater than 2 weeks, accompanied by sleep disturbances, appetite disturbances, loss of energy, decreased concentration, and/or suicidal thoughts
  – Some define PPD to occur within 4 weeks of delivery (DSM and ICD-10), others within a year of delivery (WHO definition)
  – Anxious features are more common
  – Important to ask about functioning, ability to be left alone with the baby, feelings towards the baby, worries about the baby

PACT Consortium, Lancet Psychiatry 2015
Prevalence

- Postpartum depression (PPD) affects 10 to 20% of all women of childbearing age.
  - 30% for women with MDD, 50% for women with BPAD
- Antenatal depression estimates cross a broad range. In one study of 14,540 women 18 to 50 with known past pregnancy status antenatal depression was found to be 12.4%
- Available studies suggest depression is frequently missed or under acknowledged during pregnancy

Viguera, et. al., 2011; Vesga-Lopez, 2008
The Case of Ms. A

• 29 year-old G1P1001 who had an uncomplicated vaginal delivery at 39 weeks; a wanted pregnancy.
• She is having trouble breastfeeding. The baby is jaundiced and required an additional night in the hospital to receive phototherapy. The nurse finds Ms. A. crying as she is trying to breastfeed. Ms. A also snapped at her husband when he sat down to read a magazine.
• Although Ms. A. has enjoyed holding and singing to her son, she is worried about the jaundice and whether she will make enough milk. She admits she also had an image of her son falling off the bed while changing him that upset her. She says at baseline she is a more anxious person with a tendency to pessimism and perfectionism.
Risk factors

- Depression or anxiety during pregnancy
- Family history of postpartum depression (PPD)
- Stressful life events/circumstances, history of trauma or comorbid PTSD
- Age < 18 yrs
- Inadequate social support
- Previous history of depression, PPD
- History of premenstrual mood changes
- Early weaning
- Thyroid dysfunction
- Association with PTSD and history of trauma
- Note: need for additional research re: culture, socio-economic, etc. which may not be adequately identified with current tools
Perinatal Depression and Teen Mothers: The Perfect Storm

• Higher rates of perinatal depression in adolescents
  – In minority teens, prevalence of as high as 40%
• Studies have identified psychological and social risk factors for postpartum depression in teen mothers
  – Poor social support
  – Increased stress
  – Low self esteem
  – Trauma history
• In addition, a time of biological change and hormonal transitions
Preterm Infants and Maternal Risk of PPD

• Higher rates of anxiety and depression (prevalence rate of depression of at least 50%), during the first 6 months postpartum

• Risk factors in this population:
  – Mother’s past psychiatric history
  – Previous perinatal loss
  – Psychosocial support including marital status
  – Severity of the infant’s health status
  – Degree of worry and coping skills in the mother
  – Re-hospitalization after the initial stay

Miles et al, 2007; Garel et al, 2004; Mew et al, 2003
Risks of Untreated PPD

- PPD is detrimental to the mother, her capacity to attach to her newborn and maintain relationship

- Research suggests poor bonding during this critical period can negatively impact a child’s emotional and cognitive development and may cross the child’s lifespan

- Increasing data supporting the potential for adverse effects on fetal and neonatal development

- Antenatal depressive symptoms increase the likelihood of intrauterine growth restriction and preterm birth, increases the risk of substance abuse, also associated with effect on child’s development
PPD and Lactation Failure

• Postpartum American mothers are on their own during a challenging time:
  – Recover from childbirth
  – Navigate infant feeding and attachment
  – Experience complex neuroendocrine transition from the hormonal milieu of pregnancy to lactation

• In the clinical setting, these challenges manifest as PPD and lactation failure, two problems with tremendous public health consequences
Normal Changes in the HPA Axis During the Perinatal Period

• The third trimester of pregnancy is characterized by high estrogen and progesterone levels and a hyperactive HPA axis with high plasma cortisol.

• At childbirth and during the transition to the postpartum period the following occur:
  – Estrogen and progesterone rapidly decline.
  – There is blunted HPA axis activity due to CRH secreted from the placenta and a negative feedback loop despite elevated cortisol to help with fetal maturation.
Sensitivity to Estrogen and Progesterone Changes

- Literature demonstrates that there is differential sensitivity to changing levels of reproductive hormones in some women that get PPD.
- Small study of postpartum women (1/2 with hx of PPD) given leuprolide acetate and then added back high doses of estrogen & progesterone to simulate pregnancy.
- Hormones were withdrawn and women with history of PPD developed depressive symptoms versus no women without history of PPD. Significant gene expression changes were found in estrogen responsive genes of women at risk for PPD.

Schiller et al 2015; Mehta 2014; Guintivano 2014; Bloch 2000
Heritability of Perinatal Depression and Genetic Overlap With Nonperinatal Depression


**Objective:** The authors investigated the relative importance of genetic and environmental influences on perinatal depression, and the genetic overlap between perinatal depression and nonperinatal depression.

**Method:** Analyses were conducted using structural equation modeling for 1) the lifetime version of the Edinburgh Postnatal Depression Scale in 3,427 Swedish female twins and 2) clinical diagnoses of depression separated into perinatal depression and nonperinatal depression in a Swedish population-based cohort of 580,006 sisters.

**Results:** In the twin study, the heritability of perinatal depression was estimated at 54% (95% CI = 35% – 70%), with the remaining variance attributable to nonshared environment (46%; 95% CI = 31% – 65%). In the sibling design, the heritability of perinatal depression was estimated at 44% (95% CI = 35% – 52%) and the heritability of nonperinatal depression at 32% (95% CI = 24% – 41%). Bivariate analysis showed that 14% of the total variance (or 33% of the genetic variance) in perinatal depression was unique for perinatal depression.

**Conclusions:** The heritability of perinatal depression was estimated at 54% and 44%, respectively, in separate samples, and the heritability of nonperinatal depression at 32%. One-third of the genetic contribution was unique to perinatal depression and not shared with nonperinatal depression, suggesting only partially overlapping genetic etiologies for perinatal depression and nonperinatal depression. The authors suggest that perinatal depression constitutes a subset of depression that could be prioritized for genomic discovery efforts. The study findings have direct translational impact that can assist clinicians in the counseling of their patients regarding risk and prognosis of perinatal depression.

*AJP in Advance* (doi: 10.1176/appi.ajp.2015.15010085)
**Postpartum Psychosis**

- Occurs in 1 out of 500 women, but for women with bipolar disorder 1 out of 5 women
- Rapid onset usually within 2 to 4 weeks but can occur sooner than that.
- Confused thinking, mood swings, delusions, paranoia, disorganized behavior, poor judgment, and impaired functioning
- Can appear improved and then become more depressed and psychotic
- Infanticide and maternal suicide are the most serious risks of postpartum psychosis and postpartum psychosis is a medical emergency

Suicide is the second leading cause of death in postpartum women
Screening for Postpartum Depression
Postpartum Psychiatric Illness: Detection

• PPD is frequently missed but should not be
• Overlap with “normal” postpartum experience: decreased sleep, fatigue, overwhelmed, anxiety (“normal” or not)
• Multiple contacts with health care providers provides opportunity for detection
• Edinburgh Postnatal Depression Scale (EPDS): frequently used, 10-item, self-rated
PPD, Screening, and Large Scale Efforts

• Federal legislation includes provisions for postpartum depression
  – Language on screening for PPD and increased funding for its treatment and research
• Multiple states have implemented universal screening or are in the process of implementing screening
• Political impetus to screen for PPD
Screening Instruments

• PHQ-2, PHQ-9 and GAD-7
• Edinburgh Postnatal Depression Scale (EPDS)
  – Most commonly employed screening tool for PPD
  – 10 questions self-rated instrument
  – Validated and developed specifically to identify women experiencing postnatal depression
  – English and Spanish versions
• Numerous tools have been used to assess for perinatal mania

They can be important tools to get the conversation started
They must be tied to a plan to address connecting women with care and engaging women in care
Edinburgh Postnatal Depression Scale (EPDS)

Ask patient how they have been feeling OVER THE LAST 7 DAYS, not just today
To use calculator, click on appropriate answer and score appears in box when all questions completed

1. I have been able to laugh and see the funny side of things
2. I have looked forward with enjoyment to things
3. I have blamed myself unnecessarily when things went wrong
4. I have been anxious or worried for no good reason
5. I have felt scared or panicky for no very good reason
6. Things have been getting on top of me
7. I have been so unhappy, I have had difficulty sleeping
8. I have felt sad and miserable
9. I have been so unhappy that I have been crying
10. The thought of harming myself has occurred to me

EPDS Score = /30

3 points - Yes, quite often
2 point - Sometimes
1 point - Hardly ever
0 points - Never
Postpartum Depression Screening

PPD Screening:
• Does it translate into treatment engagement?
• Revised ACOG recommendations
• Are patients referred for treatment and if so do they get better?
• Role of lay advocacy groups
For further information:
Postpartum Depression: Treatment
Treatment

- Ensure Sleep, Nutrition, Exercise
- Increase Social Supports
- Medication
- Therapy (Individual and Group)
  - Supportive and education
  - Interpersonal Therapy
  - Cognitive Behavioral Therapy
  - Dialectical Behavior Therapy
  - Dyadic work, parenting support
- Hospitalization
- ECT

Mothers face significant mixed messages in making decisions about treatments for PMAD. For example:

- “My Mother says I should just pull myself up and get out more”
- “I heard on the news that mothers taking antidepressants are more likely to have children with autism”
Treatment Recommendations: Postpartum Depression

• Moderate to severe depression
  – Consider role of antidepressants; discuss risks and benefits with mother
• Use lowest effective doses
• Consultation with experts
• Maximize non-medication alternatives
Postpartum Depression: Non-Pharmacologic Strategies

- Maximize social supports
- Psychoeducation of patient and family members
- Group therapy and support groups
- Interpersonal therapy (IPT)
- Cognitive-behavioral therapy (CBT)
  - Similar results: fluoxetine vs. 6 sessions CBT

General Pharmacologic Treatment Guidelines

• **NO** decision is risk free
• Use lowest effective dose for shortest duration possible, but goal is full symptom remission. The goal is: “The lowest amount that **GETS YOU WELL**.”
• Remember, higher doses may be needed as pregnancy progresses due to increased plasma volume and clearance rates.
• Work as a team communicating with other members of the team such as pediatrics, therapists
## Antidepressant Trials for the Treatment of PPD

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

- The treatment of PPD with synthetic forms of naturally occurring estrogen is appealing because PPD occurs in the context of estrogen withdrawal.
- Estradiol has antidepressant effects and impacts widespread regions of the cortex and limbic brain.
- Requires RCT before routine clinical use (Moses-Kolko, 2009).
- Concerns about thrombosis, affects on breastfeeding also impact use.
We are excited to announce that the postpartum depression research study at our Perinatal Psychiatry Inpatient Unit is now recruiting!

You may be eligible if you are:
- Female between the ages of 18 and 45
- Gave birth 6 months ago or less
- Currently experiencing depression after giving birth

This study requires a 4-day inpatient stay on the Perinatal Psychiatry Unit at UNC hospital. Participants will have their in-patient costs paid for by the research study and will receive up to $1,150 for participation.

For additional information, please call Holly at 919-445-0218.

You’re struggling, filled with anxiety and withdrawn from your baby. It’s not your fault.

Postpartum depression symptoms are serious and shouldn’t be ignored. Consider participating in the Hummingbird Study, a research study evaluating an investigational medication in women with moderate to severe postpartum depression.
Antidepressant Treatment During Breastfeeding

• Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum
• Few case reports of adverse effects:
  – **Doxepin**: infant had clinical effects of vomiting, sedation
  – **Fluoxetine**: Case report of high infant blood levels, colicky symptoms
    • **In women who took Fluox during pregnancy, followed postpartum while nursing**: slower infant growth in non-randomized study
  – **Citalopram**: sleep trouble in infant
  – **Nefazodone**: Case report: drowsiness, lethargy, inability to maintain body temp in a premature baby
  – **Bupropion**: possible seizure in an infant

Outstanding Lactation Resource

Drugs and Lactation Database (LactMed)

– National Library of Medicine and Toxicology Data Network
– A peer-reviewed and fully referenced database of drugs to which breastfeeding mothers may be exposed.
– Among the data included are maternal and infant levels of drugs, possible effects on breastfed infants and on lactation, and alternate drugs to consider.
Pregnancy and Postpartum: Take Home

• Use of psychotropics during pregnancy is a navigable clinical path
• Reproductive safety data for antidepressants rivals that available for almost any other class of medication taken by pregnant women
• Risks of fetal exposure to psychotropics must be weighed against growing data on toxicity of fetal exposure to untreated psychiatric disorder
• Recognition and treatment of postpartum psychiatric disorder is straightforward; access to referrals for care is an unresolved public policy issue
Allopregnanolone in Postpartum Period

Studies suggest that, even in the presence of normal absolute levels, *perinatal fluctuations in reproductive hormones may precipitate symptoms* in a vulnerable subpopulation of women as a result of changing ALLO levels.

- Cortical GABA and ALLO are reduced in postpartum women, compared with healthy women in the follicular phase
- Women with PPD show reduced resting state functional connectivity between the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal cortex in the context of the postnatal decline in ALLO
- Association of changes in ALLO levels and depressive symptoms during GnRH agonist-induced ovarian suppression and ovarian steroid addback in women with a history of PPD, but not in those without such a history

Epperson CN 2006; Deligiannidis KM, 2013; Schiller CE 2014
## Study Population

- Placebo-controlled, double-blind 1:1 randomization
- Enrolled 21 patients (10 SAGE-547, 11 placebo)
- Major depressive episode in 3rd trimester or within 4 weeks post-birth
- HAM-D $\geq 26$

## Key Endpoints

- Change from baseline in HAM-D total score at 60 hours compared to placebo
- Safety, tolerability and pharmacokinetics
202-A Results: Primary Analysis - SAGE-547 vs. Placebo
HAM-D Efficacy Results

HAM-D Total Score Over Time
- SAGE-547 (n=10)
- Placebo (n=11)

Primary Endpoint (p=0.008) at 60 hours

* = Statistical significance (p≤0.01)
202-A Results: Rapid and Sustained Improvement on MADRS
202-A Results: SAGE-547 Remission Higher than Placebo at 24 Hours through 30 Days

HAM-D Remission Rate (Total Score ≤7)

- SAGE-547 (n=10)
- Placebo (n=11)

| Time Points (hours) | 0.024 | 0.008 | 0.03 | 0.003 | 0.03 |
202-A Results: Safety and Tolerability

- SAGE-547 was generally well tolerated
  - No deaths, SAEs or discontinuations due to adverse events (AEs)
- Fewer patients reported AEs on SAGE-547 vs. placebo:
  - SAGE-547 (4) vs. placebo (8)
- Similar numbers of patients reported Nervous System Disorder AEs
  - SAGE-547 (3) vs. placebo (4)
- Equal number of patients reported the cluster of Dizziness, Sedation or Somnolence
  - SAGE-547 (3) vs. placebo (3)
- Fewer SAGE-547 patients reported Psychiatric Disorder AEs
  - SAGE-547 (0) vs. placebo (5)
  - AEs included abnormal dreams, insomnia and anxiety for placebo
Importance of Sleep

• Sleep is particularly important in women with PPD and other psychiatric disorders
• Breastfeeding can disrupt sleep
  – Recommend 4-5 hours uninterrupted sleep
  – Can be achieved by pumping during the day and having a partner or other care-giver bottle feed infant during the night, or supplement with a bottle of formula during the night
Postpartum Fathers – also to be considered...

- **Paulson (JAMA, 2010)**
  - Prevalence MDD in fathers from 1st trimester – one year postpartum: 10.4%
  - Highest in 3-6 months postpartum
  - More likely when mother is depressed

- **Abramowitz (2000, 2003)**
  - New onset OCD in pregnant/postpartum fathers
  - Ego dystonic thoughts of harming baby, wife
  - Fleeting worries likely common, sometimes reaches clinical significance
PPD ACT: A Global Smart Phone Study of PPD

• PPD ACT is the largest genetic research study to date developed by PACT Consortium
• Developed with Apple ResearchKit - launched 3/16
• More than 12,000 women enrolled, with 5,000 spit kits sent in to the NIH
• US & Aus expanding to Android version in 4/17
• New international sites - Canada, UK, Denmark
• Recruiting from low income clinics in U.S using i-touch
Resources

• US Department of Health and Human Services Office of Women’s Health “Depression During and After Pregnancy”
• Substance Abuse and Mental Health Services Administration “Depression in Mothers: More Than the Blues - A Toolkit for Family Service Providers”
Take Home Points

• One size does not fit all!!
• Critical for the well being of the woman, baby and family
• A family approach is important
• Effective treatments are readily available
  – Psychotherapy
  – Medication management
  – Social support and helping families manage the challenges of having a newborn
• Collaboration across disciplines is crucial
• Integration within treatment plans and across the continuum of care