Past, Present, and Future of Perinatal Psychiatry

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Faculty/Presenter Disclosure

• Faculty: Verinder Sharma
• Relationships with commercial interests:
  • Grants/Research Support: Lundbeck, Sage Therapeutics, Stanley Medical Research Institute, Sunovion Pharmaceuticals
  • Speakers Bureau/Honoraria: Neuroscience Education Institute
  • Consulting Fees: Otsuka, Sunovion Pharmaceuticals
Learning Objectives

• Describe major developments in perinatal psychiatry over the past 25 years
• Learn about the major gaps in our understanding of the assessment and treatment of perinatal psychiatric disorders
• Discuss how the understanding of perinatal psychiatric disorders can inform us about the etiology and management of psychiatric disorders in general
Beginning of the Journey...

Effect of pregnancy on three patients with bipolar disorder

Annals of Clinical Psychiatry, 1995

Some Definitions

Women's Mental Health
- More encompassing and includes the psychological and psychiatric aspects unique to women

Reproductive Psychiatry
- Focuses on the treatment of psychiatric disorders in women specifically during the reproductive years – premenstrual period, pregnancy, postpartum and perimenopause

Perinatal Psychiatry
- Deals with the management of psychiatric disorders in the antenatal and postnatal periods

Hippocrates

• In Cyzicus a woman gave birth with difficult labour to twin daughters, and the lochial discharge was far from good
• First day - acute fever with shivering: painful heaviness of head and neck. Sleepless from the first, but silent, sulky, and refractory...
• Sixth day - much wandering at night, no sleep
• Eleventh day - she went out of her mind and then was rational again
• Fourteenth day - many convulsions; extremities cold; no further recovery of reason...
• Sixteenth day - speechless
• Seventeenth day - death
Chapter “Mental alienation of those recently confined, and of nursing women” in the book *Mental Maladies: A Treatise on Insanity*

First to provide quantitative data - 92 cases, mania was the most common diagnosis (49 cases); relatively good prognosis as 55/92 recovered

Mental illness after childbirth more common that stats. from the mental hospital suggested
Louis-Victor Marcé

- Published a case series of women suffering from mental illness during and after pregnancy
- Gathered a wide range of data - FH, psychological patterns, social circumstances, medical and psychiatric information
- 310 cases - 9% had onset in pregnancy, 58% in the first 6 weeks postpartum and 33% after 6 weeks
- Symptoms of puerperal illness were many and varied and each symptom could be found in non-puerperal cases but the puerperal syndrome was different from non-puerperal illness

Emil Kraepelin

- Described pregnancy as having a varied impact, including a protective effect against depression in some women
- Stressed the importance of childbirth as a potent trigger for mood episodes in women with MDI; a causative factor for MDI
- Prodromal symptoms of mood and psychotic symptoms in patients with puerperal psychosis
- Stressed the importance of sleep loss as an ubiquitous and early feature of the illness

Emil Kraepelin
1856 – 1926

Sharma V and Santopinto A. German J Psychiatry 2008; 11(4)
The Asylum Era

- Puerperal Psychosis

- Postpartum Delirium
  - “The symptoms of insanity in puerperal cases almost invariably begin with loss of sleep”
  - Delirium or mania or both

- Melancholia-severe, stupor and catalepsy

- Lactational insanity

Armstrong-Jones, R. The Lancet 1923; 201(5208): 1297-8
The Picture Puzzle

- Studied 126 women with psychosis during pregnancy or in the first six months after childbirth from the Cincinnati hospital
- 252 obstetrical patients matched for race who delivered before or after the experimental group patients
- No difference in sociological factors, women with psychosis 1.5 years older (difference in fertility) and one week shorter gestation in women with psychosis
- “an etiology that is active during pregnancy but exerts its full effect only after loss of a hormone-producing organ.”

Birth of Perinatal Psychiatry

- Formation of Marcé Society in 1980
  - Ian Brockington
  - Robert Kendell
  - Channi Kumar
  - James Hamilton
  - Ralph Paffenbarger
  - George Winokur
Transitory and Shallow Syndromes

• “The many mild post-puerperal regressions, insidious disintegrations of personality and chronic psychoneurotic distortions which occur after several puerperal episodes can never be accurately evaluated, for rarely do they come to the attention of a psychiatrist, or the longitudinal story is not accurately revealed.”

• Around 1950 more interest in the study of the more common and milder disorders - abortion, perinatal death, ‘baby blues’ and postpartum depression

## DSM Specifiers

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>• The current or most recent major depressive, manic or mixed episode in major depressive disorder, bipolar I or bipolar II disorder or to brief psychotic disorder</td>
<td></td>
</tr>
<tr>
<td>• Onset within 4 weeks postpartum</td>
<td></td>
</tr>
<tr>
<td>• The current or most recent major depressive, manic, or hypomanic episode in major depressive disorder, bipolar I or bipolar II disorder or to brief psychotic disorder</td>
<td></td>
</tr>
<tr>
<td>• Onset of symptoms during pregnancy or within 4 weeks postpartum</td>
<td></td>
</tr>
</tbody>
</table>

DSM-5 Classification

- Peripartum onset specifier
  - For a manic, hypomanic or a MDE in the context of BD I, BD II, or MDD if episode onset is during pregnancy or 4 weeks postpartum

- Comorbid psychiatric disorders
- First onset vs. recurrence
- Pregnancy onset vs. postpartum onset
- Short duration of the postpartum period

Psychiatric Disorders in Pregnancy

- Cross-sectional survey of over 10,000 women in early pregnancy

<table>
<thead>
<tr>
<th>Population prevalence of a SCID disorder: 27% (95% CI 22-32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive Disorder</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
</tr>
<tr>
<td>OCD</td>
</tr>
<tr>
<td>PTSD</td>
</tr>
<tr>
<td>Eating Disorder</td>
</tr>
<tr>
<td>Bipolar I Disorder</td>
</tr>
<tr>
<td>Bipolar II Disorder</td>
</tr>
</tbody>
</table>
Anxiety Disorders in Pregnancy

• Anxiety disorders are prevalent in pregnancy; however estimates vary considerably
• Inconclusive evidence as to whether prevalence among pregnant women differs from that of non pregnant populations
• Considerable variation in prenatal course of OCD and panic disorder was found
• Substantial heterogeneity limits conclusions regarding risk factors or outcomes

Mood Disorders in Pregnancy

- Estimates of combined major and minor depression (major depression alone)
  - 6.5% to 12.9% (1.0-5.6%) at different trimesters of pregnancy and months in the first postpartum year
- Prevalence rates (95% CIs)
  - First trimester 7.4% (2.2, 12.6)
  - Second trimester 12.8% (10.7, 14.8)
  - Third trimester 12.0% (7.4, 16.7)
- Bipolar disorder
  - 5.1% (MDQ) of women at an obstetric clinic
  - 12% of women referred to a women's mental health program for psychiatric assessment during pregnancy

Bennett et al., Ob and Gyn 2004;103(4): 698-709
Gavin et al., Ob and Gyn 2005; 106(5 Pt 1): 1071-83
Merrill et al., Arch Womens Ment Health 2015; 18(4): 579-83
Case Vignette
Episode Occurrence During and After Pregnancy in Women with BD-I, BD-II or MDD

Viguera et al., Am J Psych 2011; 168: 1179-85
## Bipolar Mood Episodes During Pregnancy

<table>
<thead>
<tr>
<th>Episodes</th>
<th>BD-II (641)</th>
<th>BD-I (479)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>10.36</td>
<td>8.88</td>
</tr>
<tr>
<td>Mania</td>
<td>0.00</td>
<td>2.32</td>
</tr>
<tr>
<td>Hypomania</td>
<td>2.76</td>
<td>2.70</td>
</tr>
<tr>
<td>Mixed states</td>
<td>3.59</td>
<td>8.11</td>
</tr>
<tr>
<td>Anxiety or panic</td>
<td>3.59</td>
<td>1.54</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0.00</td>
<td>1.16</td>
</tr>
<tr>
<td><strong>All episodes</strong></td>
<td><strong>20.37</strong></td>
<td><strong>24.71</strong></td>
</tr>
</tbody>
</table>

Viguera et al., Am J Psych 2011; 168: 1179-85
## Bipolar Mood Episodes Postpartum

<table>
<thead>
<tr>
<th>Group and Clinical Type</th>
<th>BD-II (N=641)</th>
<th>BD-I (N=479)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>28.71</td>
<td>19.21</td>
</tr>
<tr>
<td>Mania</td>
<td>NA</td>
<td>7.93</td>
</tr>
<tr>
<td>Hypomania</td>
<td>2.34</td>
<td>1.25</td>
</tr>
<tr>
<td>Mixed states</td>
<td>2.50</td>
<td>6.47</td>
</tr>
<tr>
<td>Anxiety or panic</td>
<td>0.94</td>
<td>1.25</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0.00</td>
<td>1.88</td>
</tr>
<tr>
<td><strong>All episodes</strong></td>
<td><strong>34.45</strong></td>
<td><strong>37.99</strong></td>
</tr>
</tbody>
</table>

Viguera et al., Am J Psych 2011; 168: 1179-85
Early Postpartum Symptoms in Puerperal Psychosis

The most commonly recalled symptoms were:

- Feeling excited, elated or high (52%)
- Not needing to sleep or not able to sleep (48%)
- Feeling active or energetic (37%) and
- Talking more or feeling very chatty (31%)
BD and Perinatal Outcome
Population-based Studies

• BD was associated with:
  • preterm birth, severely large for gestational age (>90th percentile), congenital malformations, neonatal morbidity, and neonatal hospital readmission
  • modifiable risk factors such as obesity, DM, and HT before and during pregnancy could reduce the risk for adverse perinatal outcomes

• Women with BD, regardless of treatment with MS, were at an increased risk of:
  • delivering a preterm infant (<37 weeks gestation)
  • microcephaly
  • neonatal hypoglycaemia

Bodén R. BMJ 2012; 345:e7085
Postpartum
Postpartum Psychiatric Disorders

• Baby blues, postpartum depression and postpartum psychosis
  • Oversimplification because childbirth triggers a variety of symptoms/disorders
  • Potent and unique trigger of hypomania/mania
  • Prepartum onset
  • Lacks specificity - no treatment guidance

Brockington I. The Lancet 2004; 363(9405):303-310
Heron et al. Bipolar Disord 2009; 11(4):410-7
Linn L, Polatin P. Psychiat Quart. 1950; 24:375
Postpartum Hypomania

<table>
<thead>
<tr>
<th>Study</th>
<th>Day 3 PP</th>
<th>6 Weeks PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glover et al. 1994*</td>
<td>10.0%</td>
<td>7%</td>
</tr>
<tr>
<td>Lane et al. 1997</td>
<td>18.3%</td>
<td>9%</td>
</tr>
<tr>
<td>Hasegawa, M. 2000</td>
<td>13.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Webster et al. 2003</td>
<td>9.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Farías et al. 2007</td>
<td>20.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Heron et al. 2009**</td>
<td>11.7%</td>
<td>4.9% (8 weeks)</td>
</tr>
</tbody>
</table>

* 11% had a score of > 8 on the Highs scale on Day 5 postpartum
** 1.4% of cases had hypomanic symptoms at 12 weeks of pregnancy

Prevalence of OCD

• General population (mean = 1.08%, 12-month)
• Pregnant women (mean = 2.07%)
• Postpartum women (mean = 2.43%, 12-month)

• 2 weeks - 11%
• 6 months postpartum ½ had persistent symptoms
• 5.4% had developed new OCD symptoms
• Concomitant positive screens for anxiety and depression were predictive factors
• STAI 2 weeks (7%) and 6 months (9%)

Admissions to a Psychiatric Hospital: 2 Years Pre- and Post-Delivery

Postpartum Psychosis

- Follows 1 in 500-1000 deliveries

- Onset usually within first 2 weeks after delivery—“an odd affect, withdrawn, distracted by auditory hallucinations, incompetent, confused, catatonic; or alternatively, elated, labile, rambling in speech, agitated or excessively active.”

- Overt manifestation of BD

- PP affected 74% of mothers with BD and a first-degree relative with PP, compared with 30% of women with BD without any family history of PP

- Risk of self harm and harm to infant

- A medical emergency (hospitalization is usually required)

Phenotypical Features of Postpartum Psychosis

- Latent class analysis (130 cases of PP) — **depressive** (41%), **manic** (34%) and **atypical** (disturbance of consciousness and disorientation) (25%)

- Most common symptoms of PP—irritability (73%), abnormal thought content (72%), and anxiety (71%)

- Suicidal and infanticidal ideation was present in 19% and 8% of patients, respectively
  - Common symptoms of depressive PP: depression and anxiety, treatment was started 2 weeks later (P=.049), and more often voluntarily, than in manic and atypical women (P=.037)

Kamperman et al. Bipolar Disord 2017;Epub
Jones I, Craddock N. Br J Psychiatry 2005;186:453-454
Robertson et al. Br J Psychiatry 2005;186:258-259
Diagnosis Specific Risks of First-time Hospital Admissions 0-1 Month Postpartum Among First-time Mothers

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Time since birth of first live-born child</th>
<th>0-30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia; schizophrenia like and schizotypal disorders</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>No. of Cases</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.33 (0.19-0.59)</td>
<td>5.65 (3.47-9.20)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>No. of Cases</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.19 (0.04-0.86)</td>
<td>23.33 (11.52-47.24)</td>
</tr>
<tr>
<td>Puerperal disorders</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>No. of Cases</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td></td>
<td>38.01 (23.53-61.40)</td>
</tr>
</tbody>
</table>

Munk-Olsen et al. JAMA 2006;296(21):2582-2589
Ten thousand mothers of at least 18 years of age were screened 4-6 weeks postpartum by telephone.

Screen-positive women were invited to undergo psychiatric evaluations using the SCID in their homes.

- 14% had a positive screen (10 or more on EPDS)
- Only 2.1% did not have a psychiatric disorder
- Episode onset—40% postpartum, 33% during pregnancy, and 27% before pregnancy
- 66% women were comorbid for an anxiety disorder (5.6% as primary)

Wisner et al., JAMA Psych 2013; 70: 490-8
Postpartum Depression and BD

- 23% BD
  - BD- II – 31%
  - BD- I – 29%
  - BD NOS –19%
- Higher proportion of BD at a cut off of 13 or higher (26.7%)
- Secondary diagnoses in women with BD
  - Anxiety disorders 85%
  - Substance use disorder 12%
  - Eating disorders 3%

Wisner et al., JAMA Psych 2013; 70: 490-8
Bipolar II-A Risk Factor for PPD

• Retrospectively evaluated women with BD-I (93), BD-II (36) and MDD (444) for history of PPD

• 139, 24% had PPD
  • BD-II 50%
  • BD-I 27.5%
  • MDD 21.6%

• Women with a history of PPD were:
  • Younger
  • Younger at illness onset
  • Had more family history for BD

Mandelli et al. J Affect Disord 2016;204, 54-58
Predictors of PPD in Women with a MDD: Prospective Study

• Predictive associations between variables assessed in the 3rd trimester and the development of PPD studied in 300 women
• Women with third trimester symptoms (n = 45) versus euthymia (n = 255) had a significantly higher risk for PPD (24% vs. 11%, P = .013)
• For pregnant euthymic women, 3rd trimester total HDRS scores sig. predicted PPD (P < .0001); specifically, scores on 3 HDRS items alone - work activities, early insomnia, and suicidality
• AD use in the 3rd trimester in euthymic women did not confer protection against the onset of PPD
Familiality of Psychiatric Disorders and Postpartum Psychiatric Episodes

• ↑ relative risk of psychiatric disorders in first time mothers when first degree family members had a psychiatric disorder (hazard ratio=1.45, 95% CI=1.28-1.65)

• Highest risk when there was a family history of BD in a first-degree family member (hazard ratio=2.86, 95% CI=1.88-4.35)

• Obtaining family history of psychiatric illness, especially BD, should assist in the identification of women at risk for postpartum psychiatric disorders

Bauer AE. Am J Psychiatry 2018;175(8):783-791
Attachment Style and PPD

- Three prospective studies
- Robakis et al. found maternal insecure attachment style predicted:
  - risk of depression in the early postpartum period
  - classically recognized factors predicted depression after the 3rd month postpartum
- Ikeda et al. reported that attachment styles existing prior to pregnancy predicted:
  - Symptoms of anxiety and depression independent of the effect of comorbid mood and anxiety disorder
- Iliadis et al. neuroticism predicted PPD in non-depressed pregnant women

PPD - Recurrence and First Occurrence

• Rate of recurrence in the postpartum period
  • 41% 1 year --- 24% first 2 weeks, 67% first 20 weeks, 90% first 28 weeks

• First occurrence of MDE in the postpartum period: 5.85%
  • High risk of conversion to bipolar disorder (15%-50%)
  • Higher risk of postpartum episodes but not non-postpartum episodes

• 34.6% hypomania/mania (a score of ≥6) at ≥ 1 period PP
  24.6% at one week, 54% postpartum onset

• First occurrence of hypomania in MDD-- 6.52%

Wisner K. JAMA Psychiatry 2013; 70(5): 490–8
Sharma V. Bipolar Disord 2014;16(1):16-21
Inglis et al. Arch Womens Ment Health 2014; 17(2): 137-143
Conversion Rates to Diagnoses of BD During a 15-year Follow-up Period

- 13.87% (95% CI = 10.00-17.58)
- 4.69% (95% CI = 3.47-5.90)
- 4.04% (95% CI = 3.85-4.21)

Munk-Olsen et al. Arch Gen Psychiatry 2011;157v1-7
# Features Suggestive of Bipolarity in Women with PPD

<table>
<thead>
<tr>
<th>Illness onset</th>
<th>Younger age at illness onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>First onset of depression during the postpartum period</em></td>
</tr>
<tr>
<td></td>
<td><em>Depression onset immediately after delivery</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Illness course &amp; symptoms</th>
<th>High number of prior episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brief episodes of depression</td>
</tr>
<tr>
<td></td>
<td>Depressive episodes with free intervals</td>
</tr>
<tr>
<td></td>
<td>Seasonality of mood episodes</td>
</tr>
<tr>
<td></td>
<td>Atypical features: hypersomnia, leaden paralysis or increased appetite</td>
</tr>
<tr>
<td></td>
<td><em>Mixed depression</em></td>
</tr>
<tr>
<td></td>
<td>Psychotic symptoms</td>
</tr>
<tr>
<td></td>
<td><em>History of bipolar disorder in a first degree relative</em></td>
</tr>
</tbody>
</table>

| Treatment response            | Atypical antidepressant response: *induction of mania, hypomania or mixed depressive episodes*; poor response; rapid response; loss of antidepressant response |

Sharma et al. J Affect Disord 2017;219:105-111
Screening, Assessment and Treatment
ACOG Committee Opinion

• The American College of Obstetricians and Gynecologists (ACOG) recommends that clinicians screen patients at least once during the perinatal period for depression and anxiety symptoms using a standardized, validated tool.

• Women with current depression or anxiety, a history of perinatal mood disorders, or risk factors for perinatal mood disorders warrant particularly close monitoring, evaluation, and assessment.

• Screening by itself is insufficient to improve clinical outcomes and must be coupled with appropriate follow-up and treatment when indicated.

Number 630, May 2015
(Replaces Committee Opinion Number 453, February 2010, Reaffirmed 2016)
# Depression Screening Tools

<table>
<thead>
<tr>
<th>Scale</th>
<th>Items</th>
<th>Time (Days)</th>
<th>Scoring</th>
<th>Positive Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh Postnatal Depression Scale (EPDS)</td>
<td>10</td>
<td>7</td>
<td>30</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Postpartum Depression Screening Scale</td>
<td>35</td>
<td>14</td>
<td>175</td>
<td>Cutoff score of 80 for major PPD Cutoff score of 60 for minor or major PPD</td>
</tr>
<tr>
<td>Patient Health Questionnaire-2 (PHQ-2)</td>
<td>2</td>
<td>14</td>
<td></td>
<td>May be answered in a “yes/no” format or via a (0- to 3-point Likert scale, for a total of 6</td>
</tr>
</tbody>
</table>

1. “Have you been bothered by little interest or pleasure in doing things?”
2. “Have you been bothered by feeling down, depressed or hopeless?”

An answer of “yes” to either question warrants a third question: “Is this something you feel you need help with?”

Smith et al. Harv Rev Psychiatry 2016; 24:3, 173-187
Mood Disorder Questionnaire

Diagnosis of hypomania is positive if 7 or more items are endorsed in question 1, YES is the answer for question 2, and MODERATE or SERIOUS problem is checked for question 3. Sensitivity and specificity of these criteria compared with semi structured interviews are 73% and 90%, respectively.*

<table>
<thead>
<tr>
<th>INSTRUCTIONS: Please answer each question as best you can.</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has there ever been a period of time when you were not your usual self and...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>... you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you were so irritable that you shouted at people or started fights or arguments?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you felt much more self-confident than usual?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you got much less sleep than usual and found that you didn't really miss it?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you were more talkative or spoke much faster than usual?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... thoughts raced through your head or you couldn't slow your mind down?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you had much more energy than usual?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you were much more active or did many more things than usual?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you were much more interested in sex than usual?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... you did things that were unusual for you or that other people might have thought were excessive, foolish or risky?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>... spending money got you or your family in trouble?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>3. How much of a problem did any of these cause you - like being able to work; having family, money or legal troubles; getting into arguments or fights?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O No problem</td>
<td>O Minor problem</td>
<td>O Moderate problem</td>
</tr>
<tr>
<td>4. Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

*Manning et al. Compr Psychiatry 1997;38:102-8
Suicidality During the Perinatal Period

• UK National Confidential Inquiry-a 15-year retrospective study of all people who had been in contact with psychiatric services before suicide
  • 2% of women in perinatal period aged 16-50 years
  • 4% among women aged 20-35 years

• Lower incidence of suicide among women who have given birth during the past 12 months than that of women who have not given birth

• Perinatal suicide occurs mainly through violent methods compared to suicide in non-pregnant women

• Different risk factors for suicide attempt
  • During pregnancy: ETOH use, smoking during pregnancy and miscarriage
  • Postpartum: major depressive episode and recurrent depression

Khalifeh et al. The Lancet 2016; 3 (3): 233-42
Orsolini et al. Front Psychiatry 2016; 7: 138. 1-6
## RCTs of ADs in PPD

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study Design</th>
<th>N</th>
<th>Length (weeks)</th>
<th>Groups</th>
<th>Response Rate (% int(^{a}) vs % CNT)</th>
<th>Remission Rate (% int vs CNT)</th>
<th>Antidepressant Dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hantsoo et al. (2014)</td>
<td>DB-RPCT(^{a})</td>
<td>38</td>
<td>6</td>
<td>SER(^{a}) vs PBO(^{a})</td>
<td>59 vs 26 (p = 0.05)</td>
<td>63 vs 21 (p = 0.05)</td>
<td>SER: 50 – 200 Mean dose 100 SER and 119.4 PBO</td>
<td>Benefits of SER more pronounced when MDD onset within 4 weeks</td>
</tr>
<tr>
<td>Bloch et al. (2012)</td>
<td>DB-RPCT</td>
<td>44</td>
<td>6</td>
<td>SER + BPD(^{a}) vs PBO + BPD</td>
<td>70 vs 55 (p = 0.33)</td>
<td>65 vs 50 (p = 0.34)</td>
<td>SER: 50 – 100 Mean dose 67.5 SER and 62.5 PBO</td>
<td>SER did not add significant benefit vs PBO when added to BPD</td>
</tr>
<tr>
<td>Sharp et al. (2010)</td>
<td>RCT(^{b})</td>
<td>254</td>
<td>18</td>
<td>ADs(^{c}) vs supportive counselling</td>
<td>45 vs 20 at 4 weeks (p &lt; 0.001)</td>
<td>N/A</td>
<td>N/A</td>
<td>At 4 weeks ADs showed significant benefit but no difference seen at 16 weeks</td>
</tr>
<tr>
<td>Yonkers et al. (2008)</td>
<td>DB-RCT</td>
<td>70</td>
<td>8</td>
<td>PAR(^{e}) vs PBO</td>
<td>43 vs 31 (p = 0.94)</td>
<td>37 vs 15 (p = 0.04)</td>
<td>PAR: 10-50 Mean dose 21.1 ± 10.7 PAR</td>
<td>No significant improvements in CGI-S(^{m}) (p=0.05), HDRS(^{o}) or IDS-SR(^{o})</td>
</tr>
<tr>
<td>Wisner et al. (2006)</td>
<td>RCT</td>
<td>109</td>
<td>8 initial, 16 follow up</td>
<td>SER vs NOR(^{b})</td>
<td>80 vs 77 at 8 weeks (p = 1.0)</td>
<td>67 vs 55 at 8 weeks (p=1.0)</td>
<td>SER: 25-200 NOR: 10-150</td>
<td>No differences in response and remission between SER and NOR at 4, 8 and 24 weeks</td>
</tr>
<tr>
<td>Misri et al. (2004)</td>
<td>RCT</td>
<td>35</td>
<td>12</td>
<td>PAR vs PAR + CBT(^{f})</td>
<td>87.5 vs 78.9 (p = 0.50)</td>
<td>N/A</td>
<td>PAR: 10-50 Mean dose in monotherapy group was 35.25 Mean dose in PAR + CBT group was 32.50</td>
<td>Both PAR monotherapy and PAR with CBT were efficacious in improving mood and anxiety but no additional benefit of adding CBT</td>
</tr>
<tr>
<td>Appleby et al. (1997)</td>
<td>DB-RCT</td>
<td>87</td>
<td>12</td>
<td>FLU vs PBO: Both had 1 or 6 counselling sessions</td>
<td>N/A</td>
<td>N/A</td>
<td>20</td>
<td>Additional benefit seen from 6 vs 1 sessions of counselling or adding FLU but no advantage to adding both</td>
</tr>
</tbody>
</table>

Abbreviations: \(^{a}\)DB-RCT: double-blind randomized placebo controlled trial, \(^{b}\)RCT: randomized controlled trial (non-placebo), \(^{c}\)SER: sertraline, \(^{d}\)PBO: placebo, \(^{e}\)BPD: Brief psychodynamic therapy, \(^{f}\)ADs: antidepressant medications, \(^{g}\)PAR: paroxetine, \(^{h}\)NOR: nortriptyline, \(^{i}\)CBT: cognitive behavioural therapy, \(^{j}\)FLU: fluoxetine, \(^{k}\)int: intervention group, \(^{l}\)MDD: major depressive disorder \(^{m}\)CGI-S: Clinical Global Improvement Scale – Severity, \(^{n}\)HDRS: Hamilton Depression Rating Scale, \(^{o}\)ISD-SR: Inventory of Depressive Symptomatology-Self Report

# Preventative Effect of ADs in PPD

## Summary of antidepressant trials in the prevention of postpartum depression

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study design</th>
<th>Sample size</th>
<th>Duration (in weeks)</th>
<th>Intervention</th>
<th>Recurrence rate (%)</th>
<th>Antidepressant dose (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisner and Wheeler (1994)</td>
<td>Open trial</td>
<td>23</td>
<td>12</td>
<td>Postpartum monitoring vs. postpartum monitoring plus ADs</td>
<td>62.5</td>
<td>Known effective dose of a previously tried AD or NOR</td>
</tr>
<tr>
<td>Wisner et al. (2001)</td>
<td>DB-RCT</td>
<td>55</td>
<td>20</td>
<td>NOR vs. PBO</td>
<td>23</td>
<td>Dose gradually increased from 10 to 75 mg</td>
</tr>
<tr>
<td>Wisner et al. (2004)</td>
<td>DB-RCT</td>
<td>22</td>
<td>17</td>
<td>SER vs. PBO</td>
<td>7</td>
<td>Dose gradually increased from 25 to 75 mg</td>
</tr>
<tr>
<td>Yonkers et al. (2011)</td>
<td>Prospective cohort</td>
<td>778</td>
<td>12</td>
<td>112 women took one type of antidepressant, 16 took two types and 2 took three types</td>
<td>The hazard ratio for ADs users compared with non-users was 0.88 (95% CI = 0.51 - 1.5)</td>
<td>Doses consistent with the manufacturers’ recommended actions</td>
</tr>
</tbody>
</table>

*AD* antidepressant, *DB-RCT* double-blind, randomized controlled trial, *NOR* nortriptyline, *PBO* placebo, *SER* sertraline
Acute Treatment of Bipolar PPD

• A chart review of 18 women treated with quetiapine alone or in combination with hypnotics
  • Median: 75 mg
  • Range: 12.5 - 500 mg
• 83% were Very Much or Much Improved on retrospective Clinical Global Impression Scale
• A chart review of 26 women treated with quetiapine XR
  • Only 12 of 26 women who were enrolled in the 12-week open trial completed the study; 87% asymptomatic by week 14
  • Mean dose: 137.5 mg

Prevention of Bipolar Episodes

- Lithium is the most studied drug
- Relapse risk of PP/mania among medicated (23%) vs. unmedicated (66%)
- Antipsychotic medications, benzodiazepines, ECT are useful adjuncts
- Avoid antidepressants!

Psychotherapy

• A meta-analysis of 40 RCTs found CBT effective
• IPT
• The US Preventive Services Task Force concludes with moderate certainty that providing or referring pregnant or postpartum women at increased risk to counseling interventions has a moderate net benefit in preventing perinatal depression

Sockol LE. J Affect Disord 2015; 177: 7–21
Drugs or Depression?

• SSRIs use was associated with an ↑ risk of overall major congenital anomalies (RR 1.11, 95% CI 1.03 to 1.19)

• Congenital heart defects (RR 1.24, 95% CI 1.11 to 1.37).

• No significantly ↑ risk was observed when restricted to women with a psychiatric diagnosis (MCAs, RR 1.04, 95% CI 0.95 to 1.13; CHD, RR 1.06, 95% CI 0.90 to 1.26)

• ↑ risk of PPHN
  • Lifestyles such as smoking, alcohol use, and lack of folic acid use have been implicated in MCM

Gestational Exposure to ADs and Offspring Risk of Psychopathology

- ↑ rates of depression among adolescent children who had been exposed to SSRIs antenatally
  - Rates were higher than those whose mothers had depression but were not on ADs
- A study from Norway of 183 siblings discordant for prenatal AD exposure showed a moderate association of antenatal AD exposure and anxiety at 36 months
- A Canadian study of 45 sibling pairs discordant for AD exposure found no effect of medications on IQ or behavior at 3 to 6 years

ADs Use during Pregnancy and Intellectual Disability (ID) in Offspring

• The unadjusted RR of ID was increased in offspring born to mothers treated with ADs
• After adjustment for confounding factors, however, the study did not find evidence of an association between ID and maternal ADs during pregnancy.
• The association may be attributable to factors, such as parental age and mother’s psychiatric disorder.
Neonatal Discontinuation Syndrome

- Secondary analysis of 2 observational studies in Cleveland and Pittsburgh
  - *SRI-exposed group, mood disorder group, and comparison group*
    - Rates (defined as a score of ≥ 2 on the Finnegan Scale) were 34.1%, 35.1%, and 30.4% respectively
    - Higher rate of preterm birth (24.4%) in the SRI exposed group compared to the other groups (7.4% and 8.9%)
    - Preterm births had a significantly higher sign rate compared to full-term newborns (54% vs. 31%, p = .020)
    - Neonatal signs at 2-4 weeks were more closely associated with prematurity than with utero SRI or mood disorder exposure

Neonatal Outcomes

• Women with depression irrespective of the use of SSRIs had a significantly higher risk of developing PTB

• Neonates from women who received SSRIs during pregnancy had a significantly higher risk of RDS and significantly lower birthweight compared with controls

• The risk of PTB seems to be higher if the SSRIs were given in the third trimester compared with an earlier exposure

Eke et al. BJOG. 2016;123(12):1900-1907
Uguz et al. Compr Psychiatry 2018; 87:107-111
Brexanolone in PPD

- Active ingredient = Allopregnanolone
- Endogenous, naturally active neuroactive steroid, formed in corpus luteum of the ovary, adrenal cortex, and CNS
- Potent positive allosteric modulator of both synaptic and extra-synaptic GABA_A receptors
- Changes in the reproductive hormones during pregnancy and postpartum suggest the role of allopregnanolone in treatment of PPD
- SAGE 547 PPD Study
  - 60 hour IV infusion (titrated to 90 µg/kg/hr) in 21 women with severe PPD
  - 21 point reduction in HAM-D score for brexanolone group vs. 8.8 point reduction in placebo group at 60 hours

Kanes et al. The Lancet, 2017;390(10093):480-9
Brexanolone in PPD

• 3 RCTs covering 156 women with PPD receiving brexanolone and 111 women with PPD receiving placebo

• Sig. greater response with brexanolone infusion that started after 24 hrs (risk ratio [RR] =1.34, 95% CI 1.03-1.73) and lasted until day 7 (RR = 1.32, 95% CI 1.01-1.73). Peak was at 36 hrs (RR = 1.50, 95%CI 1.06–2.13, P = 0.02)

• greater remission starting at 24 h (RR = 1.86, 95%CI 1.03-3.34), peaking at 60 h (RR = 2.20, 95%CI 1.31-3.70) and lasting until 72 h (RR = 1.96, 95%CI 1.41-2.72). Discontinuation due to intolerability and adverse drug reactions similar with brexanolone and placebo

As of 2015, the US Food and Drug Administration (FDA) discontinued the pregnancy risk categories (ABCDX).

The A,B,C,D,X system has been replaced by the FDA Pregnancy and Lactation Labeling Rule (PLLR) that requires narrative text to describe **risk information, clinical considerations, and background data for the drug**.

The new rule includes 3 overarching categories: 1) pregnancy, which includes labour and birth; 2) lactation; and 3) females and males of reproductive potential.
Childbirth: an Unparalleled Opportunity

- Potential contributions of perinatal research to the field of mental health have yet to be realized
  - Hormonal changes, sleep loss, substance use, ADs
  - Clarify relationship between COMORBID disorders
- Primary prevention and early intervention
  - Women are routinely under the care of health professionals
  - Targeting putative risk factors—or sleep loss, substance use, and use of ADs
  - Short duration of the risk period for occurrence of postpartum mood episodes—especially hypomania or mania
- Transmission of psychopathology across generations
Perinatal Psychiatry: a Speciality or Everyone’s Business?

- Growing amount of evidence-based literature
- Hard to keep up
- Specialization leads to better care

- Better understanding – longitudinal approach
- Better overall care
- Increased awareness of the impact of childbirth

Freeman MP. J Clin Psychiatry 2014;75(10):1086-1087
Future Studies

• Effect of maternal mental illness and medications on obstetrical and neonatal outcomes
• Controlled studies of long-term neurodevelopmental outcomes in children
• Does tapering or briefly discontinuing medication toward the end of pregnancy reduce the risk of adverse effects of medications?
• Can early and appropriate intervention(s) after childbirth improve the long-term outcome of maternal mental illness?
• Biomarkers- susceptibility to hormonal change, epigenetic biomarkers
• Low serum vitamin D as a risk factor?

Robakis T et al. F1000Res 2017; Faculty Rev-916
Picture Remains a Puzzle

• ““Arranged in a tantalizing fashion, much like the pieces of a picture puzzle partly fitted together, the question remains whether all of the pieces will match, or indeed whether they are all on hand.”

Paffenbarger, 1961
Thank You