SESSION F7

Managing Psychosis during Pregnancy and Postpartum: Balancing the Risks and Benefits

Amritha Bhat, MBBS, MD

Session Description:

Postpartum psychosis is a true psychiatric emergency with implications for the mother and infant. Management of psychosis, both during pregnancy and in the postpartum period is complicated by a frustrating lack of data supporting available treatments. This presentation reviews the effects of untreated psychiatric illness and also of psychotropics when used during pregnancy and in the postpartum period. Treatment options are summarized and compared.

Learning Objectives:

Following my presentation, participants will be able to:

1. Discuss the effects of untreated psychosis on the fetus.
2. Describe the risks and benefits of available treatments for psychosis during pregnancy and postpartum.
3. Have detailed informed consent discussions with pregnant/postpartum women who need treatment with psychotropics.
MANAGING PSYCHOSIS DURING PREGNANCY AND POSTPARTUM - BALANCING THE RISKS AND BENEFITS

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Advance Practice Conference, Oct 10, 2014

Disclosure

Neither I, nor my spouse / partner have / had financial or other relationships with any commercial interest within the past 12 months.

Objectives

• To understand the risks and benefits of available treatments for psychosis during pregnancy and postpartum
• To be able to have detailed informed consent discussions with pregnant / postpartum women who need treatment with psychotropics
• To be able to manage, in an inpatient and outpatient setting, an episode of psychosis during pregnancy or postpartum psychosis

Epidemiology, Clinical features, risk factors
Pharmacotherapy – antipsychotics
Pharmacotherapy – mood stabilizers
Pharmacokinetics of pregnancy
Labor and delivery
Lactation
ECT, Investigative treatments
Prevention
Postpartum psychosis – a heterogeneous disorder

Epidemiology

Clinical Features

- Cognitive impairment
- Bizarre behavior
- Denial of pregnancy, frequently changing delusions, sometimes centered around the infant
- Atypical hallucinations
- Mood lability
- Homicidal / violent behavior – 4% infanticide

Risk factors

A true psychiatric emergency!!

Differential diagnosis

- Postpartum highs
- OCD
- CNS
- Metabolic / Nutritional
- Medications
- Immunological
- Infectious
Pharmacotherapy of psychosis in pregnancy and postpartum

Consider:
- Stage of pregnancy
- Underlying disorder and current symptomatology
- Response to past treatments
- Drug tolerability
- Breastfeeding preference.

Do:
- Avoid polytherapy
- Use the lowest effective dose
- Level 2 ultrasound – 11 – 13 weeks and at 30 weeks

Effects of the disease; Effects of the treatment

FGAs in pregnancy

- FGAs 74337 live births with 2591 first trim exposures
- RR of MM was 1.21 (=0.4% increase in absolute risk) – no pattern of MM
- Low potency more teratogenic than high potency antipsychotics
- Long term data - no cognitive sequelae at 4 years
- Transient EPS in neonate

Haloperidol

- Most safety data available
- Long term data also available
- Infrequent monitoring

- May need anticholinergics
- Limited benefit for negative symptoms
- Effective for affective symptoms?

SGAs in pregnancy

- n=151 – olanzapine, risperidone, quetiapine, clozapine
  - No differences in MM, preterm, neonatal complications or spontaneous abortions
  - Increased rate of cardiac septal defects?
  - Effects of maternal weight gain in pregnancy
  - Conflicting data about birth weight
  - Lower BSID scores at 2 months, Lower INFANIB scores at 6 months

Case example

A 26 yo G2P0 female at 7 weeks of pregnancy, with a h/o GDM has a diagnosis of Schizophrenia and is on 15 mg Olanzapine. She was switched to this medication a year ago due to hyperprolactinemia and presumed infertility secondary to risperidone. She has been asymptomatic for the past two years. Your advice to her would be to:

1) Cross taper to haloperidol which has the most available safety data.
2) Gradual taper off olanzapine and monitor closely off medications.
3) Maintain on olanzapine.
4) Cross taper back to risperidone due to risk of GDM with olanzapine.
<table>
<thead>
<tr>
<th>Study</th>
<th>Medications and numbers of subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slone et al. 1977(^{22})</td>
<td>FGAs (N = 1309)</td>
<td>No differences in rates of birth defects, perinatal mortality, birth weight, or IQ compared with the general population.</td>
</tr>
<tr>
<td>Diav-Citrin et al. 2005(^{30})</td>
<td>Haloperidol (N = 215)</td>
<td>No increased risk for birth defects</td>
</tr>
<tr>
<td>McKenna et al. 2005(^{36})</td>
<td>Olanzapine (N = 60) \nRisperidone (N = 49) \nQuetiapine (N = 36) \nClozapine (N = 6)</td>
<td>Prospective comparative study of 151 women exposed to SGAs: no increased risk for birth defects, small increased risk for low birth weight.</td>
</tr>
<tr>
<td>Manufacturers’ registries (data as reported in 2007)</td>
<td>Clozapine (N = 523) \nRisperidone (N = 250) \nOlanzapine (N = 242) \nQuetiapine (N = 446)</td>
<td>Prospective and retrospective data; no pattern of birth defects identified.</td>
</tr>
<tr>
<td>Coppola et al. 2007(^{40})</td>
<td>Risperidone (N = 713) \nwomen exposed during pregnancy; \n(N = 68) prospectively reported with known outcome.</td>
<td>No increased risk for birth defects or other adverse outcomes in the 68 cases with known outcome.</td>
</tr>
<tr>
<td>Newham et al. 2008(^{39})</td>
<td>SGAs (N = 25) \nFGAs (N = 45) \nReference group (N = 38)</td>
<td>SGA exposure: significantly higher incidence of infants being large for gestational age than in both comparison groups; mean birth weight significantly higher than those exposed to FGAs. FGAs: significantly lower mean birth weight and higher incidence of being small for gestational age than reference group.</td>
</tr>
<tr>
<td>Reis et al. 2008(^{37})</td>
<td>Exposed to antipsychotics during pregnancy (N = 570) \nFGAs (N = 460) \nSGAs (N = 101)</td>
<td>Small (OR 1.52) increased risk of defects with no pattern</td>
</tr>
</tbody>
</table>

SGA: second-generation (atypical) antipsychotic; FGA: first-generation (conventional or typical) antipsychotic
Epidemiology, Clinical features, risk factors
Pharmacotherapy – antipsychotics
Pharmacotherapy – mood stabilizers
Pharmacokinetics of pregnancy
Labor and delivery
Lactation
ECT, Investigative treatments
Prevention

Effects of the disease; Effects of the treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Obstetric outcomes</th>
<th>Teratogenicity / Neonatal Outcomes</th>
<th>Behavioral teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Polyhydramnios</td>
<td>MM 0.1 – 2.4% Ectopic, DI, hypothyroidism, floppy baby</td>
<td>None at 3 – 15 years</td>
</tr>
<tr>
<td>Valproate</td>
<td>SGA, Preterm</td>
<td>MM 8.7% NTD, cardiac, facial, genital malformations, hepatotoxicity</td>
<td>Neurocognitive sequelae, autism</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>SGA, Preterm</td>
<td>MM 2.9% NTD, facial defects, NTD, hepatotoxicity</td>
<td>Neurocognitive sequelae</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>?</td>
<td>MM 2.7% facial defects</td>
<td>Oral clefts, hepatotoxicity, rashes</td>
</tr>
</tbody>
</table>

Lithium
Most data on prophylaxis, treatment and recurrence rates after discontinuation
Long term data reassuring
May need additional antipsychotics
Breastfeeding
First trimester exposure - Ebstein’s anomaly - 0.01 – 0.05% compared to a population risk of 0.005%
Frequent monitoring

Lithium as prophylaxis
Postpartum psychosis
Relapses during pregnancy (off lithium) 0
Postpartum relapse (no lithium) 44%
Postpartum relapse (lithium prophylaxis) 0%

Monitoring guidelines - Lithium

Lithium level:
<table>
<thead>
<tr>
<th>Baseline</th>
<th>12/40</th>
<th>16/40</th>
<th>20/40</th>
<th>24/40</th>
<th>28/40</th>
<th>32/40</th>
<th>36/40</th>
<th>40/40</th>
<th>After birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li level, U/E, TTT</td>
<td>Li level, U/E, TTT</td>
<td>Lithium level</td>
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<td>Li level, U/E, TTT</td>
<td>Li level, U/E, TTT</td>
<td>Li level, U/E, TTT</td>
<td>Infant cord blood Li level, U/E, TTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US for NT</td>
<td>High res. scan – fetal echo, Doppler flow studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observe infant for withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Monitoring guidelines - antiepileptics

<table>
<thead>
<tr>
<th>Baseline</th>
<th>12/4</th>
<th>26/40</th>
<th>20/40</th>
<th>24/40</th>
<th>36/40</th>
<th>40/40</th>
<th>After birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug level</td>
<td>U/E, TPT, LFT</td>
<td>U/E, TPT, LFT</td>
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<td>U/E, TPT, LFT</td>
<td>Drug level</td>
</tr>
<tr>
<td>U/E</td>
<td>Morph scan - fetal echo</td>
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</tr>
<tr>
<td>TPT</td>
<td>Observe infant for withdrawal sedation, hepatotoxicity, anemia, skin change, hypoglycemia</td>
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### Benzodiazepines

- Teratogenicity - ± oral clefts, cardiac malformations
- Chlordiazepoxide and diazepam – safest; some data for clonazepam.
- Lorazepam - ?anal atresia
- Use in third trimester – floppy baby, hypothermia, respiratory suppression, withdrawal
- Long term – lower developmental quotient at 10 and 18 months
- Use liberally in postpartum period to ensure sleep and prevent postpartum psychosis

### Pharmacokinetics in Pregnancy

- Gastric emptying slows, small intestine and colonic transit times increase, increased GFR.
- Increase of 5 to 8 liters in total body water - higher volume of drug distribution
- Medications metabolized by cytochrome P-450 2D6 (risperidone, aripiprazole), exhibit substantially lower serum concentrations in late pregnancy

### Labor and delivery

- Premedication
- Psychiatric nurse in labor room
- Intrapartum telemetry
- Lithium during labor and delivery
- Mode of delivery
- Contraception
Baby needs attention too!!

- In utero exposure - Monitor for withdrawal syndromes
- In case of in utero exposure to Lithium, monitor renal and thyroid function
- Breast milk exposure – Monitor for side effects

Antipsychotics and lactation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Relative infant dose</th>
<th>Adverse effects</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.2 – 9.6</td>
<td>Delayed psychomotor development</td>
<td>+</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.1 – 0.2</td>
<td>Delayed psychomotor development Sedation Lethargy</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.8 – 4.7</td>
<td>Sedation Lethargy</td>
<td>±</td>
</tr>
<tr>
<td>Clozapine</td>
<td>&lt;0.1 – 4</td>
<td>Sedation</td>
<td>±</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.1 – 0.5</td>
<td>Sedation</td>
<td>±</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.8</td>
<td>Sedation</td>
<td>±</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.1 – 0.5</td>
<td>Sedation</td>
<td>±</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1.2</td>
<td>Agranulocytosis, seizures</td>
<td>-</td>
</tr>
<tr>
<td>Clozapine</td>
<td>1.0 – 1.1</td>
<td>Agranulocytosis, seizures</td>
<td>-</td>
</tr>
</tbody>
</table>

Is breast milk the best?

- Informed decision
- Single dose where possible, administered before the baby's longest sleep period
- Breast feed immediately before taking medication then avoid for one to two hours.
# Antipsychotics and lactation

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<tr>
<td>Risperidone</td>
<td>2.8-4.7</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>&lt;0.1-4</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.8</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.1-0.5</td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1.2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Clozapine</td>
<td>1.0-1.1</td>
<td>Agranulocytosis, seizures</td>
<td>-</td>
</tr>
</tbody>
</table>
Mood stabilizers and lactation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Relative infant dose</th>
<th>Adverse effects</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>3.1-69</td>
<td>Hypotonia, lethargy, hypothermia, inversion of ECG wave</td>
<td>-</td>
</tr>
<tr>
<td>Valproate</td>
<td>0.1 – 3.9</td>
<td>Thrombocytopenic purpura, anemia, and reticulocytosis</td>
<td>+</td>
</tr>
<tr>
<td>CBZ</td>
<td>1.1-7.3</td>
<td>Poor suckle, poor weight gain, sedation, transient hepatic dysfunction</td>
<td>+</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.8-21.1</td>
<td>Sedation, respiratory suppression</td>
<td>-</td>
</tr>
</tbody>
</table>

Other medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse effects</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trihexyphenidyl</td>
<td>Minor malformations</td>
<td>±</td>
</tr>
<tr>
<td>Benztpine</td>
<td>CVS malformations</td>
<td>±</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Antihistamine of choice ± oral clefts</td>
<td>±</td>
</tr>
<tr>
<td>Propranolol</td>
<td>IUGR, neonatal bradycardia and hypoglycemia</td>
<td>monitor for symptoms of beta blockade</td>
</tr>
</tbody>
</table>

Case example

- A 32 year old female, G3P2 with a history of postpartum psychosis, following both her previous two pregnancies, no mood or psychotic symptoms outside the puerperal period, and no family history of bipolar disorder presents to you in her 30th week of pregnancy, asymptomatic and on no medications. She was unable to breastfeed her first two children due to her psychotic symptoms and is insistent on breastfeeding this time. What would you advice?
  1) Start lithium in the 34th week of pregnancy and advice her not to breastfeed
  2) Start lithium immediately postpartum and monitor the neonate closely if she breastfeeds
  3) Start olanzapine immediately postpartum
  4) Start no medications but educate the family on early recognition of symptoms and keep her in frequent outpatient follow up.

ECT

- When swift improvement is needed
- Several failed trials of medications
- Intolerable medication side effects
- Catatonia

- Deaths during treatment for Postpartum psychosis:
  Before ECT use began (1927 - 1941) – 9/14
  After ECT use began (1942 - 1962) – 1/23
Complications of ECT during pregnancy

- Aspiration
- Premature labor, uterine contractions and vaginal bleeding
- Congenital anomalies in infants exposed in utero to ECT – ECT not implicated as a factor.

Investigative Treatments

- Effective in some but not all studies examining its role in puerperal psychosis
- 10mg / day oral; 17β estradiol 200 – 800 mg
- Micronized 17β estradiol 1 mg sublingual.
- Propranolol

Non medication interventions

- Psychoeducation
- Sleep
- Post discharge IOP
- Parenting enhancement
- Supportive psychotherapy, CBT, IPT, Family focused therapy once less disorganized
- In home services

Prevention of Pregnancy / Postpartum Psychosis

Episodes Limited to PP?

- Yes
  - Lithium at 34 weeks or immediately PP / Olanzapine
- Non affective psychosis – antipsychotic

- No
  - Bipolar disorder – mood stabilizer / antipsychotic
  - Avoid valproate

It can be prevented

Already diagnosed bipolar? Continue mood stabilizers. h/o postpartum psychosis? – lithium prophylaxis

Postpartum

Emphasize sleep and self care, low stim environment

Early symptoms - poor self care, confusion, difficulty caring for children postpartum highs
Take home points

- Discuss pregnancy issues with every woman of childbearing age with mood or psychotic disorder
- Emphasize importance of preconception planning
- Don’t forget about moderating factors such as tobacco, drug and alcohol use; and obesity
- Make treatment decisions on a case by case basis
- Discuss recurrence rates
- Ensure infant well being, both immediate and long term

References


Acknowledgments

Deborah Cowley, MD
My patients