Major Depression During Pregnancy

Are pregnant women protected against relapse or new onset of major depression?
Time to Relapse in Patients Who Maintained or Discontinued Antidepressant

## Relapse of Major Depression During Pregnancy

<table>
<thead>
<tr>
<th>Medication Status</th>
<th>No Relapse</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Trimester</td>
</tr>
<tr>
<td>All Women</td>
<td>115 (57.2)</td>
<td>44 (51.2)</td>
</tr>
<tr>
<td>Maintained</td>
<td>61 (74.4)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Increased</td>
<td>11 (55.0)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>Decreased</td>
<td>22 (64.7)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>21 (32.3)</td>
<td>21 (47.7)</td>
</tr>
</tbody>
</table>

**Cohen et al. JAMA. 2006.**
Relapse of Bipolar Disorder During Pregnancy

Identification and Treatment of Antenatal Depression

• Routine screening for antenatal depression has been uncommon but is changing

• Identified antenatal depression is typically untreated or incompletely treated

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

Challenges regarding management of perinatal depression are not a function of difficulties in screening.

Screening is easy; obstacles to treatment are significant – what happens to identified cases?

Are identified patients treated to euthymia if they even receive treatment?
Treatment of Depression During Pregnancy: Lessons Learned and Future Directions

- Focus of concern regarding known and unknown risks of fetal exposure to psychiatric medications is increasingly balanced by data supporting risk of exposure to disorder, stress and HPA-axis dysregulation on fetoplacental unit

- Enhanced appreciation for impact of disorder and chronic stress on long term behavioral outcomes
Relative Impact of Antidepressant Exposure vs. Depression in Obstetrical and Neonatal Outcome

• Some data support increased rates of obstetrical complications and poor neonatal outcome in depressed pregnant women

• Increased effort to distinguish impact of depression/anxiety from medication exposure on obstetrical and neonatal outcome

Impact of Maternal Depression on Obstetrical Outcomes

*Center for Epidemiologic Studies Depression Scale score in upper 10th percentile\(^1\) or Beck Depression Inventory score >21\(^2\).

†<37 wks gestational age; ‡<2.5 kg; §<10th percentile.

Treatment of Depression During Pregnancy: Take Home Message

- Absolute quantification of risk of fetal exposure is impossible
- No treatment decision is perfect
- Decisions are made with more or less complete data
Course of Anxiety Disorders Across Pregnancy: Panic Disorder

- Some studies show increased risk of new onset panic disorder in postpartum women
- The course appears variable and research to date suggests that some women may be particularly vulnerable to relapse during pregnancy

Perinatal Posttraumatic Stress Disorder (PTSD)

- Prevalence among pregnant women - 2.3%-7.7%
- Estimated new onset PTSD - 3.2%
- Childbirth may qualify as traumatic event in some cases
- PTSD related to childbirth events may lead to sexual dysfunction, avoidance of baby, fear of having more children

Ross and McLean, 2006; Ayers and Pickering, 2001
Risks of Untreated Antenatal Anxiety

• May affect maternal weight gain
• May increase risk for prematurity, low birth weight
• May increase the risk for substance abuse
• Increases the risk for postpartum depression

Ross and McLean, JCP 2006; Rambelli et al., 2009 Meshberg-Cohen and Svikis, 2007; Meshberg-Cohen and Svikis 2007; Chen et al., 2010; Lou et al., 1994; Lou et al., 1992; Acs et al., 2006.
SSRI Use During Pregnancy

• Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
  – Consistent conclusions that the absolute risk of SSRI exposure in pregnancy is small\textsuperscript{1-3}
  – Case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs\textsuperscript{4-9}

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

\textsuperscript{6} Hallberg P, Sjoblom V. \textit{J Clin Psychopharmacol} 2005; \textsuperscript{7} Wogelius P, et al. \textit{Epidemiology} 2006;
\textsuperscript{8} www.gsk.ca/english/docs-pdf/PAXIL_PregnancyDHCPL_E-V4.pdf Dear Healthcare Professional (3/17/08);
\textsuperscript{9} www.fda.gov/medwatch/safety/2005/Paxil_dearhcp_letter.pdf Dear Healthcare Professional (3/17/08)
Non-SSRIs During Pregnancy

• More limited reproductive safety data available for SNRI’s compared to SSRIs, i.e., venlafaxine, duloxetine
• Data on bupropion includes growing number of exposures supporting absence of increased risk for malformation

http://www.gsk.com/media/paroxetine/ingenix_study.pdf
Alwan et al, 2010
Antidepressant Use During Pregnancy: Lessons Learned

- Safest antidepressant to use across pregnancy is the medication that affords euthymia
- Amount of data distinguishing antidepressant compounds is very sparse with respect to teratogenic risk

Kallen, August 2008; Pharmacoepidemiol Drug Safety**
“Poor Neonatal Adaptation” and SSRI Use During Pregnancy

- Consistent data: Late trimester exposure to SSRIs is associated with *transient* irritability, agitation, jitteriness, and tachypnea (25-30%)

Clinical implication: Should women be treated with antidepressants late in pregnancy and during labor and delivery

Chambers, *BMJ*, 2009
Antidepressants During Pregnancy: Later Pregnancy Considerations

- Risk of persistent pulmonary hypertension of newborn (PPHN) with SSRIs?

- *Inconsistent findings over the last 5 years*
  - FDA communication indicates that previous estimates reflect overestimation
  - Other factors may play a role: race, high BMI, delivery by C-section
  - If there is an association, risk extremely low

• Data to support recommendations to lower antidepressant proximate to delivery are sparse
• Discontinuation of antidepressant during peripartum period may increase risk for puerperal illness
Antidepressant Treatment During Pregnancy: Take Home Points

• Safest antidepressant is the medication that affords euthymia
• Increased effort to distinguish impact of depression/anxiety from medication exposure on obstetrical and neonatal outcome
• No antidepressant is absolutely contraindicated
• Treatment across peripartum period may attenuate risk for puerperal relapse of mood
Risk of Major Depression in the Postpartum Period

Incidence (%)

- No History of Depression
- Past history major depression
- MDD during pregnancy
- Past history postpartum depression

Treatment Considerations for Women with MDD in Pregnancy

• Depression during pregnancy is strongest predictor of postpartum depression

• There are known and unknown risks associated with antidepressant use during pregnancy

• Adverse effects of depression in pregnancy on patient, infant and families

• Maternal euthymia is the most important consideration
Benzodiazepine Use in Pregnancy

First trimester exposure may be associated with increased risk for oral clefts but findings are inconsistent

Late pregnancy exposure: possible withdrawal, neonatal sedation, hypotonia, cyanosis

Avoidance in the first trimester, avoidance of polypharmacy suggested

Treatment Options During Pregnancy

- Treatment options
  - Psychotherapy (IPT, CBT)
  - Antidepressants
    - No well-controlled studies in pregnancy
    - However, available human data show no increased risk of teratogenesis or neurobehavioral sequelae
  - Electroconvulsive therapy
  - Light Therapy

IPT = interpersonal psychotherapy; CBT = cognitive behavioral therapy.

Pharmacologic Treatment of Pregnant Women with Bipolar Disorder: Weighing Imperfect Options

- Commonly employed antimanic agents are either known teratogens or have sparse available reproductive safety data
- Risks of untreated psychiatric illness
- Risk of discontinuing maintenance psychotropic medications

Antipsychotic Use during Pregnancy

Teratogenic risk

– Data support safety of typical antipsychotics with respect to teratogenicity

– FDA Drug Safety Communication: Antipsychotic drug labels updated on risk of abnormal muscle movements and withdrawal symptoms in newborns

"Antipsychotics in Pregnancy Risky for Newborns"

- FDA updated labeling on pregnancy section for antipsychotics due to risk of abnormal muscle movements
- The new labeling standards are for older antipsychotic drugs as well as newer ones.
- Based on analysis of the FDA’s Adverse Event Reporting System
- Symptoms: agitation, increased or decreased muscle tone, tremor, sleepiness, respiratory depression, and difficulty in feeding
- ? additional exposures/medical issues
Atypical Antipsychotics: Unclear Teratogenic Risk

- Postmarketing surveillance data, case reports
- In 1 prospective study, 151 pregnancy outcomes
  - Olanzapine, n = 60
  - Risperidone, n = 49
  - Quetiapine, n = 36
  - Clozapine, n = 6
  - No increased risk for major malformations
- Conclusions regarding reproductive safety not possible with available data, although no signal of teratogenicity is evident based on limited studies

National Pregnancy Registry for Atypical Antipsychotics

A **NEW** Research Study at the Massachusetts General Hospital
Center for Women’s Mental Health

To determine the safety of atypical antipsychotics in pregnancy for women and their babies

Participation will involve **3** brief phone interviews over approximately **8** months

**Call Toll-Free:**
**1-866-961-2388**
Atypical Antipsychotic Use during Pregnancy

Consider medical sequelae and impact on pregnancy: weight gain, diabetes, hypertension

Obesity - gestational diabetes, preeclampsia, and c-section

Gestational diabetes – risk factor for diabetes mellitus when nonpregnant

Hypertension – small for gestational age, preterm delivery
Lithium Use during Pregnancy: Relative Risks and Clinical Dilemmas

Ebstein’s Anomaly

*Suppes et al. Arch Gen Psychiatry. 1992.*
Lithium and Pregnancy

- Revised risk based on meta-analysis 1/1000-1/2000 (.05%)\(^1\)
- Relative risk 10-20× rate in general population (1/20,000)
- Relative vs. absolute risk

Absolute vs. Relative Risk

• Absolute risk
  – Risk stated without any context
  – The probability of something occurring
    • The likelihood of someone developing lung cancer

• Relative risk or odds ratio
  – Comparison of different risk levels
  – Ratio of incidence of disease in exposed individuals to the incidence of disease in non-exposed individuals
    • The likelihood of developing lung cancer if you have ever smoked compared to a nonsmoker
Pregnancy Registries for Anticonvulsants

• Central Registry of Antiepileptic Drugs and Pregnancy (EURAP)
• North American AED Pregnancy Registry
• U.K. Epilepsy and Pregnancy Registry
• Australian Pregnancy Registry
• Lamotrigine Pregnancy Registry
Summary of Findings Across Pregnancy AED Registries

• Valproic acid (VPA) is associated with the highest risk for all major malformations
  – Risk estimates around 10% and higher\(^1\)
  – Risk appears to be dose-dependent (>1000 mg/d); may be with LTG\(^2,3\)
  – Folic acid supplementation may not be protective against VPA-associated neural tube defects

• Risk is highest with anticonvulsant polytherapy\(^4,5\)

• Carbamazepine (CBZ) and LTG are associated with lower risk than VPA

Lamotrigine (LTG) Monotherapy Exposure: Risk for Oral Clefts

- Overall risk for major malformations with LTG approximately 2.7% across several studies

- North American Antiepileptic Pregnancy Registry showed an increased incidence of a specific malformation
  - Oral clefts: 8.9/1000 vs baseline 0.37/1000

- Finding not corroborated in other registries; further data needed

- Absolute risk remains small

Neurobehavioral Teratogenicity and Valproic Acid

Emerging data suggests that valproic acid may be associated with cognitive and developmental adverse effects.

Neurobehavioral risk with LTG unknown

Cognitive Function in 3 year olds Following Fetal Exposure to AED’s

IQ Scores of Children Who Were Exposed to Antiepileptic Drugs In Utero, According to Drug and Dose

Pharmacologic Treatment of Bipolar Disorder During Pregnancy: Take Home Messages

• Teratogenic risk and neurobehavioral toxicity of valproate make its use in reproductive age women contraindicated.

• Risk of PCOS associated with valproate use in reproductive age women in combination with neural tube defect risk and behavioral teratogenicity support this conclusion.
Gabapentin

- Lack of data
- One study: 223 women who used gabapentin in first trimester and 223 controls
- Main indications were pain and epilepsy
- Findings: Increased rates of preterm births and low birth weight but no increased risk for birth defects
- More research is needed

Clinical Implications

• Pre-pregnancy consultation
• Risk of anomalies discussed with patient in relation to background risk and specific drug(s)
• Discuss risks of untreated condition to both mother and fetus
• Discuss types of prenatal testing available
• Defer pregnancy until disease control optimal
Treatment of Bipolar Disorder in Pregnancy: Mild to Moderate Bipolar Disorder

- Gradual taper and discontinuation of antimanic prophylaxis (lithium, sodium valproate) prior to pregnancy?

- Discontinuation of mood stabilizer after pregnancy is documented? problematic with sodium valproate

- Reintroduce mood stabilizer as needed or during second trimester
Pharmacologic Treatment of Bipolar Illness during Pregnancy (continued)

- Lithium may be the safest alternative for women dependent on mood stabilizers
- Lithium nonresponders
- Consider lamotrigine monotherapy
  - Consider lamotrigine and typical antipsychotic
  - Use of atypicals across pregnancy?
- Little role for monotherapy with typical antipsychotics
Severe Bipolar Disorder During Pregnancy: Treatment Options

Consider continuation of mood stabilizer across pregnancy in women with highly recurrent illness

Frequency of use of atypical antipsychotics demands better data to inform use during pregnancy

Absolute small risk may be acceptable versus risk of bipolar relapse during pregnancy and implications for puerperal relapse of the illness
ECT During Pregnancy

- Treatment of choice when expeditious management is imperative
- Use in delusional depression, mania
- External fetal monitoring, ultrasonography
- Comprehensive treatment team

For Further Information
www.womensmentalhealth.org
References

References (Cont.)

• http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm 2011
References (Cont.)

• www.gsk.ca/english/docs-pdf/PAXIL_PregnancyDHCPL_E-V4.pdf Dear Healthcare Professional (3/17/08);