Depression In Women

Leading Cause Of Disease Related Disability Among Women In The World Today*

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Psychiatric Medications
Pregnancy and Lactation

• 500,000 pregnancies in U.S. each year involve have psychiatric illness that either predate or emerge during pregnancy

• Advising a pregnant or breastfeeding woman to discontinue medication exchanges fetal or neonatal risk of medication exposure for the risks of untreated maternal illness


Depression In Women

• Introduction/Epidemiology
• Comorbidity
• Menstrual Cycle (PMS)
• Pregnancy/Postpartum Depression
• Menopause
• Summary

Impact
Inadequate or Untreated Maternal Psychiatric Illness

• Poor compliance with prenatal care
• Inadequate nutrition
• Exposure to additional medication or herbal remedies
• Increased alcohol and tobacco use
• Deficits in maternal-infant bonding
• Disruptions within family environment

All Psychotropic Medications

- All psychotropic medications studied to date cross the placenta
- Are present in amniotic fluid
- Can enter breast milk


Genetic Variation: A Polymorphism in 5-HTT Gene

2 forms of 5-HTT gene: the short form ("s" allele) and the long form ("l" allele)

Each person inherits 1 copy of the gene from each parent; an individual may inherit: 2 short copies (s/s), 1 short and 1 long copy (s/l) or 2 long copies (l/l)

In relation to stressful life events, people with 1 or 2 copies of the short form of the 5-HTT gene exhibit more diagnosable depression and suicidality than people with 2 copies of the long allele

Interaction of 5-HTT Gene Polymorphism and Life Stress in Depression Outcomes

Results of multiple regression analyses estimating the association between number of stressful life events (between ages 21 and 26 years) and depression outcomes at age 26 as a function of 5-HTT genotype

17% s/s; 31% l/l; 51% s/l

Development of Depression: Sex and the Interaction Between Environment and a Promoter Polymorphism of the Serotonin Transporter Gene

- Boys and girls (16-19 years old) carrying short 5-HTTLPR allele react to different kinds of environmental stressors:
  a) Males affected by living in public housing rather than in own owned homes and by living with separated parents
  b) Females were affected by traumatic conflicts within the family
Development of Depression: Sex and the Interaction Between Environment and a Promoter Polymorphism of the Serotonin Transporter Gene

- Short allele response to environmental stress:
  a) With environmental stress, females tend to develop depressive symptoms
  b) Males seem to be protected from depression
- The results suggest that both the molecular and the psychosocial mechanisms underlying depression may differ between boys and girls

Mood Disorders Lifetime Prevalences

Mood Disorders Lifetime Prevalences

12-month Prevalence MDD*
6.6% of Adults in USA (13-14 million adults)

Depression In Mid Adolescence (ages 14-16*)
Increases the Risk* (ages 16-21) of:

- Later MDD, anxiety disorders -13% of cohort developed depression between ages 14 and 16
- Nicotine dependence
- Alcohol abuse or dependence
- Suicide attempt, educational underachievement
- Unemployment
- Early parenthood

(F<.05*)


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Gender Differences in Depression: Findings From the STAR*D Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Women</th>
<th>Men</th>
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</thead>
<tbody>
<tr>
<td>Prior suicide attempt</td>
<td>19.7</td>
<td>13.8</td>
</tr>
<tr>
<td>Hazardous drinking</td>
<td>13.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Hazardous use of other drugs</td>
<td>26.3</td>
<td>26.3</td>
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</tbody>
</table>

STAR*D: Sequenced Treatment Alternatives to Relieve Depression


Comorbidity

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Bulimia</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>PTSD</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Major Dep</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>PTSD+Dep</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Controls</td>
<td>28</td>
<td>4</td>
</tr>
</tbody>
</table>

ETOH Abuse ETOH Dependence

Victims of Intimate Partner Violence Comorbidity MDD and PTSD
44 women who were victims of IPV within the preceding 2 years

<table>
<thead>
<tr>
<th>Major Dep.</th>
<th>PTSD</th>
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<tbody>
<tr>
<td>44</td>
<td>50</td>
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<table>
<thead>
<tr>
<th>Lifetime Prevalence In Female Victims of PTSD</th>
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<tbody>
<tr>
<td>0.0</td>
</tr>
<tr>
<td>17.5</td>
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<tr>
<td>35.0</td>
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<tr>
<td>52.5</td>
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<td>70.0</td>
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Premenstrual Dysphoric Disorder (PMDD)

• Approximately 3-8% of women of reproductive age meet strict criteria for premenstrual dysphoric disorder (PMDD)

• 13-18% of women of reproductive age may have premenstrual dysphoric symptoms severe enough to induce impairment and distress, though the number of symptoms may not meet the arbitrary count of 5 symptoms on the PMDD list

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PMDD

• Disrupted relationships and impairment in work productivity
• Prior major depression (30% to 70%)
• Postpartum depression (29%)
• Increased risk of subsequent major depression
• Exacerbation of mood symptoms in women with primary mood disorders


PMDD
PMDD in Obstetric and Gynecologic Practices

Women were recruited from 6 primary care obstetric-gynecological practices for participation in an open trial assessing the effectiveness of a serotonin reuptake inhibitor as a treatment for subsyndromal (3-4 symptoms) and syndromal (>4 symptoms) PMDD. 904 women were screened.

<table>
<thead>
<tr>
<th>Endorsed Symptoms</th>
<th>47%</th>
<th>41%</th>
<th>36%</th>
<th>10%</th>
<th>10%</th>
<th>0.0%</th>
<th>12.5%</th>
<th>25.0%</th>
<th>37.5%</th>
<th>50.0%</th>
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<tbody>
<tr>
<td>Current PMS symptoms</td>
<td></td>
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<tr>
<td>PMS symptoms but not interested in research project</td>
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<tr>
<td>PMS symptoms not eligible for research project because of lack of symptom severity</td>
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<td>Lost to follow-up or incomplete chart</td>
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<td>PMS Symptoms and agreed to chart</td>
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PMDD Treatment Efficacy

- Accepted treatments have similar overall efficacy (60%)
- Suppression of ovulation ameliorates broad range of behavioral and physical symptoms
- SSRIs (considered first line therapy by many) most effective for irritability and anxiety symptoms

PMDD Treatment Options

- Antidepressants (SSRIs-3 have indications*)
- GnRH agonists require hormonal add-back
- Non-pharmacologic: phototherapy, aerobic exercise, cognitive behavior therapy (CBT)
- OCs - 24/4 regimen of drospirenone 3 mg and ethinyl estradiol 20 mg*

*fluoxetine, sertraline and paroxetine

*Indicated for the treatment of symptoms of PMDD in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.

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10.9% of miscarrying women experienced an episode of MDD compared with 4.3% of community women (RR 2.5)
Among miscarrying women, 72% of cases of MDD began within the first month
Among miscarrying women with a history of MDD, 54% experienced a recurrence

Increased Risk of Depression in Pregnancy*
- Prior history of depression
- Maternal youth
- Maternal isolation
- Insufficient social support
- Marital discord
- Ambivalence toward pregnancy
- Greater number of children

*20% of women affirm depressive symptoms during pregnancy

Untreated Maternal Depression
- Premature low birthweight infants
- Fetal growth restrictions
- Postnatal complication
- Newborns cry more and are more difficult to console

Depression Not Ideal For Pregnancy
- Independent of biomedical risk, perceived life-event stress and anxiety during pregnancy significantly predicted infant birth weight and gestational age
- Low birth weight and prematurity mediated by peptides derived from activated HPA axis, including ACTH and beta endorphin
- Activation of HPA axis well established in nonpregnant depressed patients

Early Pregnancy Loss
Major Depressive Disorder (MDD)
In The 6 Months After Miscarriage
(229 women evaluated following spontaneous pregnancy loss before 28 weeks gestation were compared to a population based cohort of 230 women)

• Prior history of depression
• Maternal youth
• Maternal isolation
• Insufficient social support
• Marital discord
• Ambivalence toward pregnancy
• Greater number of children


Increased Risk of Depression in Pregnancy*

Depression Not Ideal For Pregnancy


Antenatal Depression and Birthweight

There is a high prevalence of depression in south Asian women. Examined the association between antenatal depression and low birthweight (LBW) in infants in a rural community in Rawalpindi, Pakistan.

METHOD: 143 physically healthy mothers with ICD-10 depression in the third trimester of pregnancy and 147 non-depressed mothers of similar gestation were followed from birth. Infant weight was measured and information collected on socioeconomic status, maternal body-mass index and sociodemographic factors.


Postpartum Depression Risk Factors

(Major Depression within first 4-6 weeks postpartum)

- History of major depression
- History of mania (also increases risk of postpartum mania)
- History of PMDD
- Psychosocial stress
- Inadequate social support


Familiality of Postpartum Depression in Parous Female/Female Sibling Pairs (N=45) With Recurrent Major Depressive Disorder by Week of Postpartum Depression Onset

- Episodes of depression with onset within 4 weeks of delivery clustered in families, but there was no significant evidence of familial clustering of broadly defined postpartum depression (onset within 6 months).
- Among women with a family history of narrowly defined postpartum episodes, 42% experienced depression following their first delivery, whereas only 15% of women with no such family history experienced depression following first delivery.


Bipolar Disorder and Pregnancy

- Prenatal diagnosis is key; prenatal counseling is ideal
- Teratogenesis is a treatment issue (lithium, carbamazepine, valproate, lamotrigine); second generation antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole) (?)
- Breast-feeding issues (unsafe: lithium); other agents?
- Patients can be symptomatic during pregnancy; postpartum mania or depression is common (20%-45%)


Miller Lite.

Suicide Deaths and Attempts During Pregnancy and Postpartum

- >90% of suicides have a psychiatric illness
- Mood disorders associated with 60% of 80% of suicides are untreated at time of death
- Lower during pregnancy and postpartum than in the general population of women
- Suicides account for up to 20% of postpartum deaths
- During pregnancy and postpartum 5%-14% have self-harm ideation
- Best predictor of suicide appears to be prior attempt


The American College of Obstetricians and Gynecologists

- The potential risk of SSRIs during pregnancy must be weighed against the risk of depression relapse if the medication is discontinued. Untreated depression has its own risks, including low weight gain, alcohol and substance abuse, and sexually transmitted diseases, all of which have negative maternal and fetal health implications. Fetal echocardiography should be considered for women who were exposed to Paxil® in early pregnancy.


Relapse Of Major Depression During Pregnancy

- Relapsed during pregnancy: 43%
- Maintained medication: 26%
- Discontinued medication: 31%

(hazard ratio, 5.0, p<.001)

ACOG’s Committee on Obstetric Practice emphasizes that decisions about depression treatment should involve the obstetrician and the mental health clinician, along with the patient, ideally prior to pregnancy. However, because approximately 50% of pregnancies are unplanned, preconception planning for women with depression will not always be feasible, and treatment decisions about SSRIs will undoubtedly occur during pregnancy.

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Menopause, Perimenopause and Depression

(12 consecutive months of amenorrhea in the absence of causes such as pregnancy and lactation—perimenopause is 5-7 year period of transition from regular ovulatory cycles to complete anovulation)

- Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events.

- Perimenopause is associated with increased risk of recurrent depression-depression linked to bone density concerns.

Major Depressive Episodes
30-Day Prevalence By Sex

- Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events.

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Major Depressive Disorder
Factors Suggesting Lifetime Maintenance Treatment

- Prior history of depressive episodes
- Persistence of dysthymic symptoms after recovery from an episode of depression
- Presence of an additional, nonaffective psychiatric diagnosis
- Presence of a chronic general medical disorder
- Consider symptom severity and longevity

Patients experiencing an initial episode of major depression have at least a 50% chance of having a second episode, and by the third episode of major depression, there is a 90% chance of recurrence. All patients having a third depressive episode and some patients experiencing a second episode should be evaluated for maintenance antidepressant treatment.


Resources
Pregnancy & Lactation Medication

- http://www.obfocus.com/resources/medications
- http://www.perinatology.com/exposures/druglist

Depression In Women
Summary

- Mood disorders are linked to the reproductive life cycle
- Pharmacologic treatment has benefit and risks (pregnancy, lactation)
- PMDD appears to respond to SSRIs and venlafaxine
- Hx of mood disorder confers increased risk of postpartum mood syndromes
- Remission is the goal
- Perimenopause is a zone of increased risk
- SSRIs ideal (comorbidity experience)
- phototherapy, exercise and natural or nutritional remedies deserve more attention
- Risk/benefit ratio is key to all clinical decisions

Neonatal Outcomes After Prenatal Exposure to Selective Serotonin Reuptake Inhibitor Antidepressants and Maternal Depression Using Population-based Linked Health Data

- Neonatal Distress
  - Treated with SSRIs: 13.9%
  - Not Treated with SSRIs: 7.8%
- Jaundice
  - Treated with SSRIs: 9.4%
  - Not Treated with SSRIs: 7.5%
- Feeding Problems
  - Treated with SSRIs: 3.9%
  - Not Treated with SSRIs: 2.4%


SSRI/SNRI and Neonates Discontinuation Syndrome? Risks Should Be Described In Patient Labeling, FDA’s Pediatric Subcommittee Of Its Anti-infective Drugs Advisory Committee Recommended June 9, 2004

- “Neonates exposed to SSRI/SNRI late in 3rd trimester have developed complications requiring prolonged hospitalization, respiratory support, tube feeding. AE may arise immediately upon delivery.***”

Persistent Pulmonary Hypertension of Newborn

- Occurs in as many as 6.8 of 1000 live births
- Mortality is approximately 10% to 20% with high-frequency ventilation, surfactant, inhaled nitric oxide, and extracorporeal membrane oxygenation but is much higher when these therapies are not available

SSRIs and PPHN*

- Infants exposed to SSRIs in late pregnancy may have an increased risk
- In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not** been exposed to antidepressants during pregnancy

**.37% of 377 women whose infants had PPHN vs. .07% of controls

*July 2006 from package insert


Paroxetine and Risk of Cardiovascular Malformations

- Infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs)*
- Pregnancy precaution revised from Pregnancy Category C to Pregnancy Category D (indicative of positive evidence of human fetal risk) as well as placement of the usage in pregnancy language in the WARNINGS section of the label.

*US United Healthcare Study increased risk of CV malformations: Paxil 1.5% vs. 1% who were dispensed other antidepressants (5956 mothers who were dispensed paroxetine or other antidepressants)

Effects of Antenatal Depression and Antidepressant Treatment on Gestational Age at Birth

Participants included 49 women with major depressive disorder who were treated with antidepressants during pregnancy (group 1), 22 women with major depressive disorder who were either not treated with antidepressants or had limited exposure to them during pregnancy (group 2), and 19 healthy comparison subjects (group 3).

Effects of Antenatal Depression and Antidepressant Treatment on Gestational Age at Birth (before 37 weeks gestation)

Participants included 49 women with major depressive disorder who were treated with antidepressants during pregnancy (group 1), 22 women with major depressive disorder who were either not treated with antidepressants or had limited exposure to them during pregnancy (group 2), and 19 healthy comparison subjects (group 3).

**Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects**

- Like Louik, et al. found no significant association between SSRI use overall and congenital heart defects
- Louik et al. showed significant associations between SSRI use overall and congenital heart defects (paroxetine and RVOFTO) and neural tube defects
- Alwan et al. did find maternal SSRI use was associated with anencephaly, craniosenosis and omphalocele-yet absolute risks were small

**Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects**

- Specific SSRIs may increase the risk of specific birth defects-further studies with sufficient power needed
- Absolute risk of these rare defects are small
- Risk/benefit ratio is key

**Bipolar Disorder Medications & Pregnancy**

<table>
<thead>
<tr>
<th>Generic Name/Pregnancy Category</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium-D (CV-Ebstein’s)</td>
<td>Mania, Maintenance</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)-D (NTDs)</td>
<td>Mania, Epilepsy, Trigeminal Neuralgia</td>
</tr>
<tr>
<td>Divalproex (Depakote)-D (NTDs, DD) (antenatal folate recommended)</td>
<td>Mania, Mixed Episodic, Epilepsy, Migraines</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)-C</td>
<td>Schizophrenia, Mania, Mixed Episodes, Maintenance (bipolar)</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)-C</td>
<td>Schizophrenia, Mania, Mixed Epipides, Bipolar Depression</td>
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<tr>
<td>Risperidone (Risperdol)-C</td>
<td>Schizophrenia, Mania, Autism (agitation)</td>
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<tr>
<td>Ziprasidone (Geodon)-C</td>
<td>Schizophrenia, Mania, Mixed</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)-C</td>
<td>Schizophrenia, Mania, AntID augment</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)-C</td>
<td>Epilepsy, Maintenance Phase Bipolar I Disorder</td>
</tr>
</tbody>
</table>

**Effects of Antenatal Depression and Antidepressant Treatment on Gestational Age at Birth**

Participants included 49 women with major depressive disorder who were treated with antidepressants during pregnancy (group 1), 22 women with major depressive disorder who were either not treated with antidepressants or had limited exposure to them during pregnancy (group 2), and 19 healthy comparison subjects (group 3).
Atypical Antipsychotic Administration During Late Pregnancy: Placental Passage and Obstetrical Outcomes

- Exposure to lipophilic fetal tissue such as lung and brain
- Statistical tendencies toward more low birth weight babies (4-8%, p<.06) and neonatal intensive care unit admissions (7-9%, p<.09)
- Haloperidol-40 years of clinical use may be preferred but has limitations: anticholinergics may be teratogenic, therapeutic benefits other than possible symptoms of psychosis limited

METHOD: The authors conducted a prospective observational study of women treated with an atypical antipsychotic or haloperidol during pregnancy. Maternal and umbilical cord plasma samples collected at delivery were analyzed for medication concentrations. Placental passage was defined as the ratio of umbilical cord to maternal plasma concentrations (ng/ml).

Antidepressants and Breast Milk

- Nortriptyline, paroxetine, and sertraline may be preferred choices in breastfeeding women
- Current data do not support monitoring breast milk levels in individual patients
- When administrating valproate to nursing mothers, clinical pediatric status, LFTs and platelets should be carefully monitored

Antidepressants and Breast Milk

- Of drugs currently used, fluoxetine produces the highest proportion (22%) of infant levels that are elevated above 10% of the average maternal level
- Citalopram indicates produce elevated levels in 17% of infants

Safety of Antidepressant Drugs During Pregnancy

- Transient neonatal symptoms common after use of antidepressants in late pregnancy
- Few firm data available on possible impact on the long-term neuropsychological development of the infants
- Magnitude of actual contribution from drug therapy is unclear; underlying pathology of the mother may explain part of the anomalies
- When non-pharmacological treatments are not enough, the relatively small risk with drug therapy has to be weighed against the considerable risk for a relapse of the disease if therapy is interrupted

References:
- Newport, D. J., M. R. Calamaras, et al. (2007). "Exposure to lipophilic fetal tissue such as lung and brain: statistical tendencies toward more low birth weight babies (4-8%, p<.06) and neonatal intensive care unit admissions (7-9%, p<.09)."
- Haloperidol-40 years of clinical use may be preferred but has limitations: anticholinergics may be teratogenic, therapeutic benefits other than possible symptoms of psychosis limited.