Antidepressants in Pregnancy
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PMADs- Perinatal Mood and Anxiety Disorders

- Antenatal Depression (AND)
  - Baby blues
- Postpartum depression (PPD)
- Postpartum psychosis
- *Perinatal PTSD, *Panic Disorder
- *Perinatal OCD (obsessive compulsive disorder)
- Perinatal Bipolar Disorder –mania, hypomania

*also treated with antidepressants during pregnancy
Treatment of PMADs
(Perinatal Mood and Anxiety Disorders)
• 50% pregnancies in the U.S. are unplanned
• SSRI’s by far are the most studied medication in pregnancy than any other class of medication >200,000 pregnancy outcomes studied.
• Antidepressants are the 2nd most prescribed class of drugs in the world.
• Estimated 6.5% of pregnant women take an antidepressant in 1\textsuperscript{st} trimester, decreases to 4% 2\textsuperscript{nd} 3\textsuperscript{rd} trimester
Literature regarding Antidepressants in Pregnancy - Strengths and Limitations

- Studies are observational -retrospective, rely on prescription databases, teratology services, birth registries or population records of birth defects
  - Thus little is known about medical, psychiatric, addiction condition of the mother or other exposures
  - Gold Standard-Prospective RCTs do not include pregnant women and may never.
  - Observational studies are designed to show association but not causation
- Literature changes often
- Animal studies tell us very little
- Many negative reports never replicated or not published.
- Selection Bias: Positive studies over reported.
  - Law firms seized this information – widely publicize.
  - Hot topic in the media
  - Physicians and patients use the media reports or advertisements from law firms to inform their judgment.
# Summary of Fetal Outcome Studies on Selective Serotonin Reuptake Inhibitors—Selective Serotonin Norepinephrine Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Negative studies that show no malformation risks (n)</th>
<th>Positive studies that show malformation risk (n)</th>
<th>Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine (15)</td>
<td>Paroxetine (8)</td>
<td>Congenital anomalies (general)</td>
</tr>
<tr>
<td>Fluoxetine (12)</td>
<td></td>
<td>Cardiovascular gastroschisis anencephaly</td>
</tr>
<tr>
<td>Citalopram (9)</td>
<td></td>
<td>Anencephaly, cardiovascular</td>
</tr>
<tr>
<td>Sertraline (8)</td>
<td></td>
<td>Cardiac, general</td>
</tr>
<tr>
<td>Fluvoxamine (7)</td>
<td>Sertraline (2)</td>
<td>Cardiovascular, craniosynostosis</td>
</tr>
<tr>
<td>Escitalopram (4)</td>
<td>Fluoxetine (3)</td>
<td>Cardiovascular, neural tube defects</td>
</tr>
</tbody>
</table>

Untreated Depression
- Inadequate maternal weight gain
- Poor maternal self-care
- Substance use
- Preeclampsia
- Impaired fetoplacental function
- Fetal distress
- Cesarean delivery
- Neonatal care unit admittance
- Postpartum depression

Antidepressant Use
- Miscarriage
- Preterm birth
- Low birth weight
- Small for gestational age
- Long-term neurodevelopmental abnormalities?
- Cardiac defect
- Major malformation
- Persistent pulmonary hypertension?
- Postnatal adaptation syndrome

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FDA categories in pregnancy outdated, little clinical use

A. Controlled studies fail to demonstrate risk in humans

B. No controlled studies in women, animal studies do not show risk or adverse effect in animal studies.

C. Adverse effects in animals, no controlled trials in women or no studies.

D. Evidence of human risk exist

X. Contraindicated
Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

CURRENT LABELING

8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers

NEW LABELING
(effective June 30, 2015)

8.1 Pregnancy includes Labor and Delivery
8.2 Labor and Delivery includes Nursing Mothers
8.3 Females and Males of Reproductive Potential

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Pregnancy Sub-section

- Fetal risk summary
- Clinical considerations
- Review of human data
- Drug registry information
- A general statement regarding background risk of loss and malformations in pregnancy

Lactation Sub-section

- Risk summary
- Clinical considerations
- Review of human data

(FDA, 2014)
Basic Prescribing Guidelines based on data limitations

- Use older medications over newer medications
  - ~800 cases can detect a two fold increase in malformation risk
  - ~10 year window to obtain this data
- “Unknown” does not mean safe
- Human data over animal data
- Know how to quickly access resources
  - [www.womensmentalhealth.org](http://www.womensmentalhealth.org)
  - [reprotox.org](http://reprotox.org) through Micromedex
Duloxetine Hydrochloride was also found in...

- Toxicology and Exposure Information (3)
- Disease Information (0)
- Reproductive Risk Information (2)

Reprotox (1)
- Duloxetine

Teris (1)
- Duloxetine
DULOXETINE

Reprioxine®

Quick take: Based on experimental animal studies and limited human reports, duloxetine exposure is not anticipated to increase the risk of congenital anomalies. Warnings about possible adverse neonatal effects are based on one case report and experience with other serotonin reuptake inhibitors. A pregnancy registry has been established.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor marketed in the US as Cymbalta for the treatment of depression, generalized anxiety disorder, diabetic neuropathic pain, fibromyalgia, and chronic musculoskeletal pain, and, in Europe, for stress urinary incontinence.

Experimental animal studies

In preclinical studies reported in the product labeling, no malformations were produced in rats and rabbits at maternal dose levels of 45 mg/kg/day, although fetal weight reduction was seen at these exposure levels. These dose levels are 7 (rat) and 15 (rabbit) times the recommended human dose on a surface area basis. In another study, 30 mg/kg/day (5 times the human dose on a surface area basis) produced fetal weight reduction in rats.

An abstract describes a study in rats in which treatment with 10 mg/kg/day during pregnancy resulted in alterations in behavioral testing in the offspring suggesting an increase in reactivity (1). There was no effect on survival or reproductive performance of these offspring.

Human pregnancy reports

Among 761 women enrolled in 8 randomized controlled pre-marketing trials of duloxetine (dose range 40-120 mg/day, mean exposure 49.5 days) there were 20 pregnancies (13). No malformations were reported. A prospective multinational study using data collected from teratology information services and pharmacovigilance centers found no differences in the rates of major malformations when comparing 208 pregnancies with exposure to duloxetine (2.17S in the first trimester) to 208 pregnancies with exposure to other antidepressants and 208 with non-teratogenic exposures (14). In the duloxetine group there were 165 live births including 3 malformations (hydrocephalus, renal agenesis, and clubfoot) for a rate of 1.8%. While 51 women took duloxetine throughout pregnancy, the majority (N=155) discontinued it within the first trimester; 2 women took it only in the 2nd and 3rd trimesters. Data were collected between March 2010 and April 2012, using maternal self-report in most cases, with outcome data obtained within 3 months of delivery.

A report from the Swedish Medical Birth Register (through 2011) on 206 infants whose mother filled a prescription for duloxetine in the first trimester and 173 whose mothers filled a prescription in the 2nd or 3rd trimester found no increased risk of congenital malformations (15). Other potential adverse pregnancy outcome data were not reported for individual medications. A study from the manufacturer used the FDA Adverse Events Reporting System and the Lily Safety System (16). Among 253 pregnancy exposures reported prospectively to the manufacturer, there were 8 congenital anomalies, 3 stillbirths, 41 miscarriages, and 143 normal outcomes. The remainder of the cases were complicated by a so-called postpartum condition, prematurity, ectopic pregnancy, or a post-term delivery. Following an analysis of the FDA database, the authors concluded that there was no disproportionally reporting of adverse events for duloxetine (N=175) compared to other antidepressants. No conclusions as to true frequency of adverse pregnancy outcomes can be derived from either database.
The Risks of Untreated PMADs
Risk of Untreated Antenatal Depression

(Fields 2006, 2011)

- Decreased prenatal care, poor nutrition
- Increased maternal use of tobacco, alcohol or cocaine
- Maternal suicidal/homicidal behavior increased
- Premature delivery, Lower birth weight and smaller head circumference
- Increased risk of preeclampsia, diabetes, cesarean delivery
- Developmental delays in the infant
- Poor maternal infant bond and infant attachment
- Decreased rates of breastfeeding
- Increase in affective disorders in children and adolescents (Buss 2012)
- Alterations in the right amygdala of the neonate (Graboi 2013)
- Maternal Treatment of antenatal depression appears to help normalize cortisol levels (O’Hara 2013)
Risk

Benefit

=  ?
Pharmacologic Risks during Pregnancy

1st Trimester - Morphologic risk
- <2 weeks  No maternal/ fetal exposure
- 1-5 weeks  Neural Tube Development
- 3-8 weeks  Cardiac
- 6-9 weeks  Lip and Palate

2nd-3rd Trimester (> 14 weeks)
- Neonatal Behavioral/Cognitive/Affective Risks
- Neonatal effects (toxicity/withdrawal)
- Maternal side effects
- Maternal Outcomes (preeclampsia, PTL)
History of SSRI’s and Teratogenesis

- Prozac launched 1980’s
- Baseline rate of birth defects 3-4%. Cardiac Anomalies 1%
- 1980-2004 “No increased risk for malformations”
- 2005: GSK report to FDA – Paxil leads to increased risk of VSD. Retrospective database.
- 2005 – 2013: 30+ studies examining link between SSRI’s and malformations, mainly Heart Defects - conflicting results.
- 6/2014 Huybrechts NEJM Cohort 64,000 women exposed to AD “No substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester of pregnancy.”
Prenatal SSRIs and risk of ASD (Autism Spectrum Disorders)

• 4 studies thus far: 2 show an association (OR 2.54, 2.2), 2 did not
• Confounding factors that were difficult to/not controlled for
  – underlying burden of maternal psychiatric illness (OR 1.54)
  – underlying indication for antidepressant use
  – genetic history
  – maternal illness/stress during perinatal period
• ASD also linked to SSRI use before – but not during — pregnancy (OR 1.46)
• Summary - The rise in ASD disorders have been consistently linked to maternal obesity, advanced maternal and paternal age, gender, family history, family history of ASD and maternal and perinatal stress. Risk with SSRIs likely either no increased risk or minor increased risk after confounding factors controlled for.

(Croen et al 2011, Rai et al, 2013)
Poor Neonatal Adaptation Syndrome (PNAS)

- Approximately 25% of infants with late SRI exposure. (Also seen with AP, BDZ, opiates withdrawal)
- Unclear if withdrawal or toxicity
- Tremor, restlessness, increased muscle tone and crying.
- Symptoms largely resolved with minimal interventions <48 hours
- (Warburton 2010)– Stopping AD at 38 weeks did not improve neonatal outcome.
- PNAS occurs in general population approx. 10%
SSRI’s and PPHN Persistent Pulmonary HTN Newborn 2006 FDA issues a public health advisory

(Chambers 2006): SSRI’s taken >20 weeks gestation may be associated with 1% absolute risk of PPHN (OR 6.1) N=377 infants. Case controlled, retrospective.

(Andrade 2009, Wichman 2007): 2 larger studies have found no association between antidepressant use during pregnancy and PPHN,

(Kallen 2008) showed a much lower risk marginally clinically significant than the 1% originally reported. (Odds Ratio 2.01) SSRI was associated with a 0.15% Absolute risk (1.5 per 1000)

C-section and BMI had greater risk than SSRI exposure.

SSRI exposure may lead to small increased risk for PPHN, but not as high as Chambers original report.
SSRI and Preterm labor/ Miscarriage/ Birth Weight/ APGAR

- **Miscarriage** - Although controversial, several studies link increase risk of miscarriage with SSRI use from 8 vs. 12%. Poorly controlled studies. Anderson et al (2014) compared miscarriage rate of women who continue SSRI use versus those that discontinue SSRI’s prior to pregnancy. No increased rate of miscarriages. (N=1,279,840)

- **Decreased gestational age** (3-5 days) linked to SSRI use

- **LBW** risk appears clear but incidence small– Seen in illness state and with SSRI exposure. 75g lower birth weight.

- **APGAR** Decrease of 0.5 points on 1 and 5 minute Apgar
• English & Spanish Support
• Area Support Coordinators
• Educational DVD
• Chat with an Expert Phone Forums

www.postpartum.net
1-800-944-4PPD
Oregon PSI Resources

- **Baby Blues Connection** - Portland/Vancouver
  www.babybluesconnection.org
  1-800-557-8375

- **Hope for Mothers and Esperanza para las Madres** - Albany
  Samaritan Albany General Hospital
  Telephone: 541-812-4475

- **Life with a New Baby** and **Curso Madres y Bebes** -- Marion/Polk
  503-485-2191 or 503-910-4337

- **Well Mama Oregon** - Lane County
  www.wellmamaoregon.org

- **Well Mama** – Linn Benton
  www.wellmama.net

- **Moms-2-Moms** -- Klamath Falls
  541-281-8686
  Oct 2014
  W Davis, PhD
WOMEN’S MENTAL HEALTH AND WELLNESS

Our women’s mental health clinicians provide evaluation, counseling, and treatment for many challenges that affect women, including perinatal mental health concerns, stress related disorders, relationship and sexual concerns, prenatal loss and bereavement.

Our counselors are an integral part of the OHSU Center for Women’s Health, working together with their physician colleagues and providing support for patients, their partners and families.