The Impact of Prenatal SSRI Exposure: Sensing the Signal Through the Noise

Tamar L Gur, MD, PhD
Assistant Professor
Depts of Psychiatry and Behavioral Health, Neuroscience
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Disclaimer Statement

- I have no financial ties to any of the treatments mentioned in this talk
- I have no conflicts of interest to disclose
Objectives

- Understanding of the impact of maternal depression and anxiety on the developing human
- Understanding of the preclinical literature regarding the effect of prenatal selective serotonin reuptake inhibitors (SSRI) on the developing Central Nervous System (CNS)
- Understanding of the clinical literature on the effect of SSRIs on the developing CNS
- Be able to use that information to weigh the risks and benefits of initiating SSRI treatment in pregnant women.
Psychiatric illnesses have a developmental component.

Exposure to adversity during development is a risk factor for schizophrenia, depression, anxiety.

Do events that happen in utero contribute to long term behavioral changes?
Hypotheses

Nature

Pendulum Swing

Nurture
Barker Hypothesis

- Fetus makes physiological (mal)adaptations in response to changes in its environment to prepare itself for postnatal life.
- Increased risk of stroke, DM, HTN, obesity with low birth weight.
- These changes may include epigenetic modification of gene expression.
What this is NOT:

How was school, dear?
Clinically Relevant Question
Why is this important?

- Major depressive disorder (MDD) is widespread in women with a lifetime prevalence of 16.5 %
- Up to 15 % of women will suffer from depression while pregnant
- 3% of pregnant women take antidepressants and the number of women being treated is increasing
  - Most commonly selective serotonin reuptake inhibitors (SSRI)
- Pregnancy is a major reason many women stop receiving antidepressants

Kessler et al. 2005; Evans et al. 2001; Bennet et al. 2004; Gavin et al. 2005; Oberlander et al. 2006; Bakker et al. 2008; Petersen et al. 2011
How do we weigh out the risks and benefits?
Neonatal Outcomes

- Maternal Depression itself is bad for the developing human
- Associated with
  - Pre-eclampsia
  - Intrauterine Growth Restriction
  - Preterm Delivery
  - Neonatal complications
  - Compromised fetoplacental function

Reviewed in Gentile, 2010
Behavioral outcomes

- Antenatal stress and anxiety contribute to increased anxiety and altered stress response in children
  - Daily hassles to proximity to the World Trade Center attack
- Increased risk of depression in children exposed to prenatal maternal depression

O'Connor et al., 2005, 2012; Davis and Sandman 2012; Pearson et al., 2013
What about SSRIs and pregnancy?

- Common adverse consequences:
  - Preterm birth
  - Poor neonatal adaptation syndrome
    - Irritability, sleep disturbances, tremor, rigidity, and limpness
    - Increased risk of hospitalization within 1st year (bronchiolitis- unclear link)
  - Literature does not support an association between maternal SSRIs as a class and major congenital malformations
    - Cardiac septal defects (fluoxetine, paroxetine)

# Preterm Delivery

## Logistic Regression of Risk in a Psychiatric Sample

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio [95% CI]</th>
<th>$X^2$, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental Abruption</td>
<td>8.73 [1.08 – 70.3]</td>
<td>$X^2=4.14$ p=.04</td>
</tr>
<tr>
<td>Maternal Infection (Other than Chorioamnionitis)</td>
<td>7.19 [1.75 – 29.5]</td>
<td>$X^2=7.49$ p=.006</td>
</tr>
<tr>
<td>History of Previous Preterm Delivery</td>
<td>4.64 [2.04 – 10.6]</td>
<td>$X^2=13.4$ p=.0003</td>
</tr>
<tr>
<td>Zolpidem Exposure during 3rd Trimester</td>
<td>3.31 [1.39 – 7.90]</td>
<td>$X^2=7.35$ p=.007</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>2.90 [1.07 – 7.87]</td>
<td>$X^2=4.35$ p=.04</td>
</tr>
<tr>
<td>Weekly Avg. HamD for 3rd Trimester* (16-20 vs. 0-15)</td>
<td>2.76 [1.15 – 6.64]</td>
<td>$X^2=5.17$ p=.02</td>
</tr>
<tr>
<td>SRI Antidepressant Exposure during 3rd Trimester</td>
<td>2.31 [1.14 – 4.67]</td>
<td>$X^2=5.40$ p=.02</td>
</tr>
</tbody>
</table>

HamD=Hamilton Rating Scale for Depression  
SRI=Serotonin Reuptake Inhibitor

N=841

Gur TL et al. Unpublished Data
How do we weigh the risks and benefits?
Focus on Serotonin

Serotonin

- Attention
- Cognition
- Mood
- Arousal
- Stress Response

Lucki 1997; Anderson 2004; Hendrick et al. 2003; Rampono et al. 2009
Serotonin and Development

- Serotonin acts as a trophic factor overseeing cell division, neuronal migration, and synaptogenesis...
- ...Which is why you can believe that altering it during critical windows could lead to childhood and adult mental illness
  - Changes in receptors in the offspring
  - Changes in transporters in the offspring
  - Changes in overall serotonin levels
- SSRIs can cross placenta, capable of impacting developing CNS

Gaspar 2003; Reviewed in Bonnin 2011; Oberlander et al., 2009; Kiser et al. 2012; Kalueff 2010
Big Question

- Is developmental exposure to SSRI causing behavioral changes?
  - Preclinical Literature
    - Depression
    - Anxiety
    - Social Behaviors
  - Clinical Literature:
    - Affective Disorders
    - Social Behavior
    - HPA Axis
    - Psychomotor Development

Gaspar 2003; Reviewed in Bonnin 2011; Oberlander et al., 2009
How Clinicians Imagine it is Done
Preclinical Studies

Elevated Plus Maze

Forced Swim Test

Social Interaction Paradigm
Mouse gestation = 18-21 days

Rat gestation = 21-23 days

3rd trimester

Puberty

Adult

Gur et al. 2013
Depression

- Increased depressive like behaviors in offspring exposed to developmental SSRI (n=4)
Anxiety

- Increased anxiety like behaviors in offspring exposed to developmental SSRI in half of the studies reviewed (n=13)
Social Behavior

- Decreased social behaviors in 3 out of 4 studies
Does this translate?

- Reliance on animal models to predict both the safety of prenatal drug exposure has a mixed and unfortunate history

- Thalidomide
  - Teratogenicity is well documented in humans, rats did not demonstrate physical deformities

- Benzodiazepines
  - Rodent studies demonstrated an increased risk of cleft palate
  - Human studies did not find an increased risk of cleft palate

Greek et al. 2011; Miller and Becker, 1975; Wee and Zimmerman, 1983; Culiat et al. 1995; Condie et al. 1997; Rosenberg et al. 1983; Dolovich et al. 1998
Antidepressant use in pregnancy may raise autism risk

Health.com  By Anne Harding, Health.com
July 6, 2011 9:22 a.m. EDT

SSRIs and Birth Defects

WHAT ARE SSRIS?
Selective serotonin reuptake inhibitors (SSRIs) are the most popular antidepressant drugs used to treat depression and other mental illnesses worldwide. Scientists believe that depression can be triggered by a lack of the chemical serotonin, and these drugs make higher levels of serotonin in the brain to combat the issue.

USE
SSRIs are popular in the United States. In 2010, more than 24.4 million prescriptions were filled for general health.

RISK
Research from linked SSRIs use during pregnancy and birth defects, including persistent pulmonary hypertension of the newborn, cleft lip with or without cleft palate, heart defects, pyloric stenosis, idiopathic thrombocytopenia, and birth defects. These are not separate and well-controlled studies of SSRIs in preganant women.

IN 2005, DANISH RESEARCHERS FOUND THAT IF A MOTHER TAKES AN SSR IN DURING THE FIRST TRIMESTER, HER CHILD HAS 45 PERCENT GREATER CHANCE OF DEVELOPING A HEART PROBLEM THAN THE GENERAL POPULATION.

Women who take more than one SSRIN during the first trimester have a 1-in-4 chance of having a baby with a heart defect.

Anti-depressants in pregnancy

- increased miscarriages
- heart malformation
- lung disorder
- poor health

SOURCE: UBC Therapeutics Initiative

The Ohio State University
Wexner Medical Center
Clinical Outcomes

- Affective Behaviors

  - Autism Spectrum Disorder

  - HPA Axis

  - Psychomotor Development
Affective behaviors

- Internalizing behaviors: depression, irritability, anxiety, emotional reactivity, and withdrawal
- Measurements used: Child Behavioral Checklist, Child teacher report form, Observation, Connor Parents rating scale
- 5 studies exist, to date
**Results**

- No evidence of increased anxiety with SSRI exposure
  - 5 y.o. oldest examined
  - Small sample sizes

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<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Treatment</th>
<th>Measures Used</th>
<th>Outcome examined</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misri et al., 2006</td>
<td>22-exposed to SSRI, 14-unexposed to SSRI</td>
<td>SERT, FLX, PAROX</td>
<td>Child Behavioral Checklist, Child teacher report form</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Oberlander et al, 2007</td>
<td>4 year olds: 14-unexposed 22-exposed</td>
<td>SERT, FLX, PAROX</td>
<td>Child Behavioral Checklist</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Oberlander et al., 2010</td>
<td>3 year olds: 42-unexposed 22-exposed</td>
<td>SERT, FLX, FLVX, PAROX, CIT, VEN</td>
<td>Child Behavioral checklist, observation,</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Nulman et al., 2012</td>
<td>Children: 62-ven exposed, 62-SSRI exposed 54-Depressed unexposed, 62 non-depressed non-exposed</td>
<td>SERT, FLX, FLVX, PAROX, CIT, VEN</td>
<td>Child Behavioral checklist, Connor Parents rating scale Weschler IQ</td>
<td>Anxiety, IQ</td>
<td></td>
</tr>
<tr>
<td>Pedersen et al., 2013</td>
<td>Children 4-5 year old: 127- SSRI exposed 98-Depressed unexposed, 723 non-depressed non-exposed</td>
<td>SERT, FLX, FLVX, PAROX, CIT, VEN, TCA</td>
<td>Strengths and Difficulties Questionnaire</td>
<td>Emotion, social behavior, attention</td>
<td></td>
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Gur et al., 2013
Clinical Outcomes

- Affective Behaviors
- Autism Spectrum Disorder
- HPA Axis
- Psychomotor Development
Increase in number of children diagnosed with ASDs

Appropriate to questioning the role of prenatal factors

Serotonin plays a role in complex social behavior
  - Contributions from the amygdala, hippocampus, medial prefrontal cortex, sensory cortex, insular cortex, and orbitofrontal cortex each responsible for various components

Multitude of behaviors- aggression, maternal attachment, social play

Olsson and Phelps 2007; Homberg 2007
Autism Spectrum Disorders

1. Children with ASD were twice as likely to have had a mother who was taking an SSRI immediately prior or during pregnancy than children in the comparison group (6.7 % vs. 3.3 %)

2. Maternal depression associated with increased risk of ASD (OR 1.49, 95% CI 1.08-2.08) but only in subset with antidepressant (SSRI+other) exposure
   - It accounted for 0.6% of the cases of ASD

Croen et al., 2011; Rai et al., 2013
Clinical Outcomes

- Affective Behaviors
- Autism Spectrum Disorder
- HPA Axis
- Psychomotor Development
Importance of the HPA Axis

- MDD frequently occurs in the context of acute or chronic stress
  - Relative hyperactivity of the HPA axis
- Intact HPA axis is important in regulating stress response
- Increased risk of depression in children of depressed mothers may be through suboptimal development of the fetal HPA axis
- HPA axis dysfunction could lead to
  - Decreased stress tolerance
  - Medical problems including metabolic and cardiovascular disease

Claes et al., 2009; Glover et al. 2010
The HPA axis in Pregnancy

- CRH released from placenta into maternal and fetal compartments
- Cortisol increases throughout pregnancy
  - 11BHSD2 protects developing fetus
- 5-HT is also involved in regulating neurons releasing CRH in the hippocampus

Sandman et al 2009
Prenatal SSRI Exposure and the HPA Axis

- Decreased:
  - Basal salivary cortisol in infants at 3 and 6 months of age
  - Cord blood cortisol
  - Corticosteroid binding globulin found to be increased in newborns
- This mirrors preclinical findings
- Suggest that perhaps prenatal exposure buffers the infant from increased HPA reactivity
  - Indicates that the developing HPA axis is influenced by prenatal SSRI exposure

Oberlander 2008; Brennan et al. 2008; Pawluski 2012; Davidson et al. 2009
Clinical Outcomes

- Affective Behaviors
- Autism Spectrum Disorder
- HPA Axis
- Psychomotor Development
Psychomotor development

- Well established tests
  - APGAR
  - Bayley Scale Psychomotor development
  - Brazelton Neonatal Behavioral Assessment Scale

- Provides immediate time point to examine neurobehavioral effects of intrauterine exposure
## Results

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<tr>
<td>Casper et al., 2003</td>
<td>Infants: 13 unexposed 31 exposed</td>
<td>SERT, FLX, FLVX, PAROX</td>
<td>APGAR, Bayley Psychomotor development</td>
<td>Psychomotor development</td>
<td></td>
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<tr>
<td>Casper et al., 2011</td>
<td>Infants: 55 exposed</td>
<td>SERT, FLX, CIT, PAROX</td>
<td>APGAR, Bayley Psychomotor development</td>
<td>Psychomotor development</td>
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<td>Pederson et al., 2010</td>
<td>Danish national birth cohort</td>
<td>SSRI</td>
<td>Postnatal interview at 6 and 19 months of age</td>
<td>Psychomotor development 6 months 19 months</td>
<td></td>
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<tr>
<td>Mulder et al., 2011</td>
<td>Fetuses: exposed-96 unexposed-37 Controls-130</td>
<td>SERT, FLX, FLVX, PAROX, CIT, VEN</td>
<td>Ultrasound during pregnancy</td>
<td>Intrauterine motor activity</td>
<td></td>
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<tr>
<td>Zeskind and Stephen</td>
<td>Newborn Exposed-17 Unexposed-17</td>
<td>SERT, FLX, CIT, PAROX</td>
<td>Neonatal Behavioral Assessment Scale</td>
<td>Motor activity at birth</td>
<td></td>
</tr>
<tr>
<td>Nulman et al., 1997</td>
<td>Children Tricyclic-80 Fluoxetine-55 Unexposed-84</td>
<td>TCA FLX</td>
<td>Bayley Scales of Infant Development  McCarthy Scales of Children's Abilities Reynell Developmental Language Scales</td>
<td>Psychomotor development</td>
<td></td>
</tr>
<tr>
<td>Nulman et al., 2002</td>
<td>Children Tricyclic-46 Fluoxetine-40 Unexposed-36</td>
<td>TCA FLX</td>
<td>Bayley Scales of Infant Development  McCarthy Scales of Children's Abilities Reynell Developmental Language Scales</td>
<td>Psychomotor development</td>
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<tr>
<td>Suri et al., 2011</td>
<td>Infants Exposed-33 Unexposed-16 Control-15</td>
<td>FLX, SERT</td>
<td>Brazelton Neonatal Behavioral Assessment Scale</td>
<td>Psychomotor development</td>
<td></td>
</tr>
<tr>
<td>Salisbury et al., 2011</td>
<td>Infants Exposed-36 Unexposed-20 Control-56</td>
<td>SERT, FLX, FLVX, PAROX, ESCIT, VEN</td>
<td>NICU Network Neurobehavioral Scale</td>
<td>Quality of movement Attention</td>
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Gur et al., 2013
SSRI and Psychomotor Development

- Some domains of behavior and neurodevelopment may be adversely affected by SSRI exposure while others are more sensitive to the effects of maternal mental illness.

- Unclear what the long term consequences of alterations of motor activity at birth might be.
  - Follow up at older age suggests it resolves.

- Recent finding suggest that prenatal SSRI exposure is protective in regards to externalizing behavior, attention, and language development.

Weikum et al, 2013a, b
Summary

- **Preclinical findings:**
  - Increase in depression-like behavior
  - Equivocal finding with anxiety
  - Alteration in social behaviors
  - Methods used and the findings not uniform

- **Clinical findings:**
  - No evidence of alterations in affective behavior
  - 2 studies suggesting increased risk of ASD
  - HPA axis appears to benefit
  - Bidirectional alteration of psychomotor development
Conclusions

- These data are not robust enough to discourage use of SSRIs during human pregnancy
  - Known adverse effects of maternal mental illness on pregnancy outcomes and infant neurodevelopment

- Future research should focus on:
  - Consistent animal model
  - Prospective human studies with larger samples
  - Meaningful translational targets
Treatment Strategy

Already Pregnant
- Risk/Benefit
- Best Medicine
- Effective Dose
- Frequent F/u
- Empower if had D/C

Planning Pregnancy
- Medication Needed?
  - Yes
    - Risk/Benefit
    - Best Medicine
    - Effective Dose
    - Frequent F/u
  - No
    - F/U

Mom:
- Monitor for PPD
- Allow Breastfeeding if desired

Baby:
- Monitor for PPHN, Poor Neonatal Adaptation Syndrome
- Appropriate weight gain
Future directions

Modified from Bohacek et al. 2013
Coming soon….

Stress (10 d)
Antidepressant – 6 weeks
Preconception
Gametes

Behavioral testing

Gametes & Brain
Of the offspring
Resources

Women’s Behavioral Health at OSU
- Drs Newport, Carpenter, Hyman, Horseman

WBH Website
http://psychiatry.osu.edu/wbh/

MGH web
http://womensmentalhealth.org/
"My obstetrician recommended I nurture it in the interest of science."
So far so good