Neonatal Effects of Maternal Usage of....

SSRIs

(Selective Serotonin Reuptake Inhibitors)

&

SNRIs

(Serotonin-Norepinephrine Reuptake Inhibitors)

Important Implications of Maternal-Child Caretakers

Neonatal Effects of Maternal SSRI/SNRI Usage….

Research has been focused in four areas….

- Congenital defects from 1st trimester exposure
- Neonatal behavioral effects from 3rd trimester exposure
- Maternal & fetal outcomes resulting from stopping anti-depressant therapy during pregnancy
- Implications for breastfeeding

Depression and Pregnancy

- **Depression affects ~ 14-23% of pregnant women (ACOG)**
- **1:4 women will develop depression in their lifetime.**
- **Depression and anxiety is often treated with SSRI/SNRIs.**

  Many other conditions treated with these Rx include mood disorders, personality disorders, OCD, ADHD, chronic neuropathic pain, smoking and eating disorders (indefinite treatment).
- **SSRI/SNRI use in pregnant women for depression or other conditions is unknown and there are limited long-term studies. But estimates of 13-30% of pregnant women will ultimately use these medications during a pregnancy.**
- **SSRI use in the perinatal period doubled between 1995-2005.**
- **Women who are taking SSRI/SNRIs who are pregnant or intend on becoming pregnant should discuss the situation with their OB doctor due to potential risks to the fetus and infant.**

SSRIs

(one of most commonly used class of antidepressants, increases levels of serotonin by inhibiting its reuptake)

SSRIs (risk of Postpartum hemorrhage, premature birth, LBW) include…

- **Celexa, Cipramil, others (citralopram)**
- **Lexapro, Cipralex, Esertia (escitalopram)**
- **Prozac, Sarafem, others (fluoxetine)**
- **Luvox, others (fluvoxamine)**
- **Zoloft, others (sertraline)**
- **Paxil (paroxetine) – AVOID, risk of heart defects**

SNRIs

(class of antidepressants that increase levels of serotonin & norepinephrine by inhibiting their reuptake)

SNRIs (? risk of PP hemorrhage) include…

- **Effexor, Effexor XR** (venlafaxine
- **Pristiq** (desvenlafaxine)
- **Meridia, Reductil** (sibutramine) – used for weight loss
- **Cymbalta (duloxetine) – SSRI/SNRI**
- **Serozone (nefazodone) –** less sedation than Effexor or Cymbalta

Others……

- **Wellbutrin, Zyban (Bupropion)--**works by inhibiting the reuptake of dopamine, serotonin, and norepinephrine; possible association with heart defects?
- **SYMBYAX--** has been shown to affect the three neurotransmitters that are important in the treatment of bipolar depression: serotonin, dopamine and norepinephrine
- **Bicifadine --** works by inhibiting the reuptake of serotonin, and norepinephrine and to a lesser extent dopamine, used to treat diabetic neuropathy as well
- **Tricyclic antidepressants** (Pamelor)-- ? associated with increased CHD, PP hemorrhage

AVOID….. **Paxil** due to increased risk of fetal heart defects) &
MAOIs (monoamine oxidase inhibitors) due to decreased fetal growth.

Possible Issues: SSRIs *combined* with Other Medications?

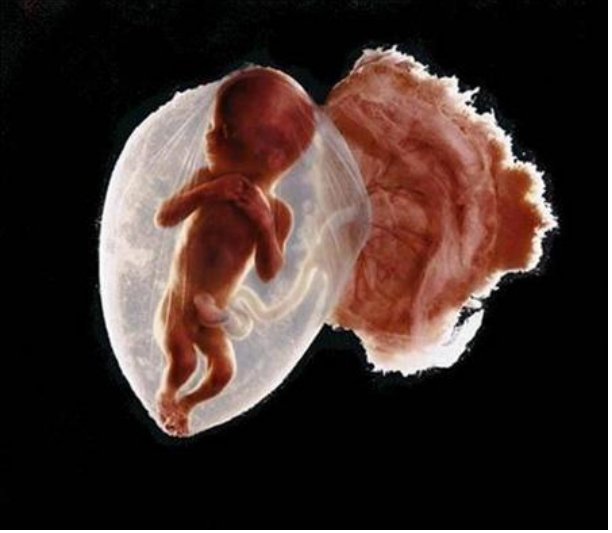
Clinical Case:

Multiple SSRI / SNRIs in same patient seems to worsen the infant's symptoms/adaptation

Maternal Zoloft 100mg/day & Ambien nightly. There have been cases of neonatal flaccidity reported in infants whose mothers have been receiving Ambien. A particular infant presented flaccid & apneic in the delivery room nearly necessitating intubation and then unable to wean off Nasal CPAP for several days before "woke up."

SSRI/SNRIs

- SSRI/SNRIs cross the placenta easily which has prompted research on the effects on infants, sometimes very serious adverse effects. They may also cross into breast milk.
- Several studies looked at the association of cardiac malformations, oomphalocele, craniosynostosis and SSRIs but meta-analysis did not find significant association except…..
- Paxil (Paroxetine has been re-classified as FDA Pregnancy Category D due to significant risk of ASD & VSD.
- All other SSRI/SNRIs remain Category C.



SSRI/SNRIs
(continued)

- All drugs in these classes have some reports of discontinuation symptoms….no SSRI/SNRI is without the possibility of these symptoms
- Severity of symptoms is related to cord blood levels (which are rarely measured).
- Maternal use of SSRI/SNRIs during and after pregnancy may result in adverse effects on newborns due to withdrawal effects following intrauterine exposure or toxic effects from ingestion of SSRIs in breastmilk or rarely possible teratogenic effects on the fetus.

SSRI/SNRIs

(continued)

A significant number of infants born to mothers taking SSRI/SNRIs during late pregnancy display clear signs of antidepressant withdrawal indicating that these drugs can penetrate the fetal brain in utero at biologically significant levels causing potential neurologic adverse effects.

SSRI/SNRIs
(continued)

- In studies, 20-30% of newborns whose mothers took antidepressants during pregnancy experienced neonatal abstinence syndrome. There are 4 categories of symptoms: CNS (depression followed by excitation), GI, Autonomic & Respiratory.
- Spontaneous reporting of adverse reactions generally underestimates the risks associated with use (often suspicious behavior noted at birth but not reported such as that of late preterm infant).
- There is Level 2 (mid-level) evidence that SSRI exposure during pregnancy is associated with increased risk of LBW, preterm birth, fetal death & seizures.

SSRI/SNRIs
(continued)

- Neonates exposed to SSRI/SNRIs late in 3rd trimester have developed adverse effect resulting in prolonged hospitalization, respiratory support, IV therapy, tube feeding, etc.
- Adverse effects may arise immediately upon delivery or later
- Reporting consistent with SSRI/SNRI Discontinuation symptoms or direct toxic effects of the drug (adults experience dysequilibrium, N/V, flu-like symptoms, sensory disturbances, sleep disturbances, neuropsychiatric symptoms, worsening of previous or development of new neuropsychiatric symptoms.
- In some cases, neonatal adverse events are consistent with Serotonin Syndrome (adults experience convulsions, disorientation, cognitive impairment, hypertonia, rigidity, myoclonus, hyperreflexia, paresthesia, autonomic instability, temperature instability, respiratory distress, tachypnea, rigors, chills, diaphoresis, tachycardia)

SSRI/SNRIs
(continued)

- May be more accurate to refer as **Neonatal Serotonin Toxicity** as it mimics serotonin toxicity related to CNS over-stimulation rather than withdrawal – jittery, irritable, tachypnea, temperature instability, tremors, even seizures, increased muscle tone, hyperactive Moro.
- **Best description is that SSRI/SNRI exposure leads to problems of…**

"Delayed Neonatal Adaptation"

SSRI/SNRIs

(continued)

Date of Onset: Adverse effects may arise immediately upon delivery or shortly thereafter during transition

Range: Symptoms of central serotonin overstimulation generally last 0-4 days but can last up to 14 days (one report of 4 weeks).

Resolution: Generally 2-3 days, most recover after a brief period of intensive intervention but symptoms may last up to 2 weeks.

Effects of SSRI exposure may occur postnatally through breastfeeding transfer and may result in sleepiness, decreased alertness, irritability and/or poor growth.

SSRI/SNRIs
(continued)

- All neonates exposed to SSRI/SNRI in the last trimester should be followed closely for adaptation/withdrawal symptoms after birth.
- It is essential that the delivery room team be aware of any history of maternal SSRI/SNRI use and be prepared for a symptomatic infant. Many institutions require an NNP or House Pediatrician attend delivery if Mom taking anti-depressants.
- A minimum of 48 hours of close monitoring is recommended. These neonates are not candidates for early discharge.
- Follow-up of exposed infants is needed to check effects of prolonged exposure.

Some of our experiences:

- **Delivery Room:** Awake & alert but apneic or infrequent shallow breaths requiring prolonged tactile stimulation, FFO2, mask CPAP or bag/mask ventilation.
- **Well Baby Nursery/Full Term Nursery:**

  Jittery, slow to warm up, low blood sugar, poor feeding
- **SCN / NICU:**
  - Mom on Celexa: Infant grunting in WBN, then had hypoventilation with "sigh breaths" for ~ 12 hours & monitored in SCN → then able to transition back to WBN
  - Respiratory Distress and/or PPHN (infant with mild HMD requiring oxygen per NC for 7-10 days – PPHN)
  - Irritability, Poor Feeding requiring IV fluid supplementation, Temperature instability, Jitteriness, Seizure-like behavior (mega-workup)

Neonatal Issues

- Without recognition the infant may do poorly at birth due to initial birth depression/apnea
- Without recognition (and sometimes even with), the infant often undergoes a costly and unpleasant evaluation of his/her symptoms to be sure that SSRI/SNRI exposure is the cause of the symptoms
- This is emotionally disturbing to the parents and utilizes precious medical resources
- Premature infants seem to be more susceptible

Consequences of SSRI/SNRI Exposure

- **Miscarriage:** A study in Canadian Medical Association Journal finds that the use of depression medications during pregnancy raises overall risk of miscarriages by up to 68%.
- **Low Birth weight / SGA:**
  - 7.2% for babies of non-depressed moms
  - 10.9% for babies of moms on SSRIs
  - 13.6% for babies of depressed moms, not on SSRIs
- **Premature Birth**
  - 6-7% for moms without depression
  - 9-20% for moms with depression taking SSRIs or not
- **SCN / NICU Admission:**
  - 7 % for babies of non-depressed moms
  - 9 % for babies of depressed moms
  - 16 % for babies of moms taking SSRIs
- **Lactation Onset Delayed in Mothers on SSRIs**
  - Average Lactation Onset Time 69.1 hours (no SSRIs)
  - Average Lactation Onset Time 85.8 hours (on SSRIs)

Symptoms of SSRI/SNRI Exposure

- **Respiratory Distress:** respiratory depression, apnea, tachypnea, bradycardia **(6.3%)**
- **Persistent Pulmonary Hypertension (PPHN):** up to 6X as likely (especially Paxil, Zoloft)
- **Prolonged QT Interval** (marker for sudden death)

  10% of exposed infants seem to have a temporary prolongation which generally resolves by 48 hours of age….more studies needed
- **Congenital Heart Defects:** 2 studies show that women who took Paxil during the first 3 months of pregnancy were 1.5x more likely to have a baby with a heart defect (often ASD, VSD)

Symptoms of SSRI/SNRI Exposure

- **Temperature Instability: hypothermia, fever**
- **Feeding & Digestive Disturbances, Poor Feeding – breast or bottle, need for tube feedings, vomiting, jaundice**
- **Hypoglycemia (19%)**
- **Lethargy, Sleepiness, Sleep disorders**
- **Hypotonia / Hypertonia, Hyperreflexia**
- **Apnea, Respiratory Distress, cyanosis and/or PPHN**

Symptoms of SSRI/SNRI Exposure (con't)

CNS U/S Symptoms (depression→excitation):

- **Irritability, Restlessness, Agitation**
- **Staring, no crying, high-Pitched Cry, Constant Crying Tremulousness, Shivering, Jitteriness (one study demonstrated persisting tremors @ 6-14 months of age)**
- **Heightened Startle, Increased Motor Activity**
- **Marked Extensor Posturing with Back Arching**
- **Rigidity, Tremors, "Seizures"**

Admission to SCN or NICU (13%) for neonatal complications

- **Prolonged hospitalization (22%) but severe issues rare (3%)**
- **No significant increase in major anomalies**

OB Considerations

- Morbidity of depression (to mother, neonate, family, society) is an important consideration.
- Discontinuation of SSRI/SNRIs during pregnancy may increase risk of relapse of major depression, especially postpartum depression
- Healthcare providers and patient must weigh potential risks & benefits for mother and neonate when deciding about treatment. When treating pregnant woman with SSRI/SNRIs (especially during the 3rd trimester), carefully consider potential risks and benefits

OB Considerations: Effects of Untreated Depression during Pregnancy

- **Maternal Effects:** **Non-compliance with prenatal care & poor self-care, poor nutrition, poor appetite, poor weight gain, Postpartum depression, Preeclampsia, poor sleep, Self-medication with alcohol, tobacco & drugs, spontaneous abortion, bleeding, C/S, early termination of breastfeeding, difficulty bonding, suicide.**
- **Fetal Effects:** **NICU Admission, behavioral problems in childhood, Low Apgar scores, Lower dopamine and serotonin levels, Preterm birth, LBW, SGA, Smaller head circumference**

OB Considerations

- Some physicians may consider tapering SSRI/SNRI late in 3rd trimester and then reduce risk of relapsing depression by resuming SSRI/SNRIs after delivery
- Lack of consensus about interpretation and management of these neonatal adverse effects
- Controlled studies are needed!

Long-Term Effects of SSRI/SNRI exposure:

- Has not been thoroughly examined in humans
- Level 2 (mid-level) evidence up to age 71 months showing NO deficiencies in cognition, language development or behavior.
- Level 3 (lacking direct evidence) showing evidence of delays in fine motor movement and persisting tremulousness.
- Animal studies have shown permanent changes in specific parts of the brain & altered behavior in adulthood after perinatal exposure to SSRI/SNRIs.
- Rodent studies have demonstrated that early exposure to some anti-depressants can result in persistent abnormalities in adult behavior.

Long-Term Effects of SSRI/SNRI exposure (con't)

- Some data argues that exposure to SSRI/SNRIs at an early age can disrupt normal maturation of serotonin system.
- Recent preliminary information suggests a possible link between women taking certain anti-depressants and autism in children: serotonin works differently in adults, where it acts as a neurotransmitter, primarily carrying signals from one nerve cell to another, than in infants where it acts like a growth factor telling the brain how to develop.
- Rats given SSRIs during the first few weeks of life (a period of rat brain development equivalent to the 3rd trimester. The rats showed autism-like symptoms: antisocial behavior, avoidance of new stimuli, inability to play and lifelong decreased sexual interest. More importantly, increasing or decreasig the dose respectively worsened or lessened autism-like behavior. In post-mortem analysis, the rats also showed brain abnormalities compared with normal rat brains.
- Research with long term follow-up is needed!

Long-Term Effects & Future Recommendations: Breastfeeding

- **Delayed Onset of Lactation for Mothers on SSRIs**
  - **Important to keep in mind to facilitate successful feeding. Breastfeeding while taking SSRI/SNRIs may be associated lethargy & reduced growth according to a few studies**
- **Breastfeeding recommendations are unclear and controversial when compared with the benefits of breastfeeding.**

  Recent Zoloft with 7 days of O2 therapy, fully breastfed, re-hospitalized for failure to thrive?
- **Some suggest breast feeding helps minimize withdrawal symptoms and that the Failure To Thrive (FTT) is less of a problem. But this may depend on which SSRI/SNRI & what dose the mother is prescribed.**

Long-Term Effects & Future Recommendations: Breastfeeding (con't)

- **Prozac is the SSRI most likely to be transferred into breast milk.**
- **Current recommendation is minimization of effects by using the lowest effective maternal dose, while breast milk transfer for symptomatic infants can be treated by stopping or reducing the dose of SSRI/SNRIs, combining breast & bottle feeding or by discontinuing breastfeeding**
  - **Recent 34 week infant whose mother was bipolar, depressed and anxious & was taking Lexapro, Trazadone & Buspar. Infant had very odd behavior, strange apnea/bradycardia which necessitated HHNC for 21days & Caffeine. Infant was hospitalized for over a month. Eventually stopped all BRM due to persistence of symptoms.**
- **Currently, most believe that SSRIs / SNRIs appear safe for nursing mothers**
  - **In Thomas Hale MD's book Medications and Mothers' Milk lists most SSRIs / SNRIs as L2 (Safer) or L3 (Moderately Safe)**

Long-Term Outcome

- **Long term influence on cognitive & emotional development remains unclear.**

- **Fortunately, with attentive care during pregnancy, at birth and during the neonatal period, long term neonatal outcomes after SSRI/SNRI exposure appears generally good.**