SELECTIVE SEROTONIN REUPTAKE INHIBITOR

ANTIDEPRESSANT USE IN PREGNANCY

& PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Figure 1. Legal Advertisements

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OBJECTIVES

1. Review depression in pregnant women & management of depressive episodes
2. Review risks and benefits of pharmacologic treatment of depression in pregnant women
3. Evaluate risk of persistent pulmonary hypertension of the newborn (PPHN) with selective serotonin reuptake inhibitor (SSRI) use in pregnancy
DEPRESSION IN PREGNANCY

Introduction\textsuperscript{1,2}
- Rates of depression are higher during pregnancy than at any other point during a woman's life
- Depression is one of the most frequently encountered medical complications during pregnancy and postpartum
- Between 14\% and 23\% of pregnant women will experience a depressive episode while pregnant
- Rates of relapse in pregnant women with a history of recurrent mood disorder are about 50\%

Definition\textsuperscript{3}
DSM IV criteria for major depressive syndrome or an episode is defined by five or more of the following symptoms listed below present most of the day, nearly every day for a minimum of two consecutive weeks. At least one symptom is either depressed mood or loss of interest or pleasure.

- Depressed mood
- Loss of interest or pleasure in most or all activities
- Insomnia or hypersomnia
- Change in appetite or weight
- Psychomotor retardation or agitation
- Low energy
- Poor concentration
- Thoughts of worthlessness or guilt
- Recurrent thoughts about death or

Pathophysiology\textsuperscript{1}
Pregnancy is a major physiological life event. The biological changes during pregnancy also have a direct effect on mood state. For example:

- Concentrations of female specific sex steroids are raised during gestation \rightarrow modify parts of the brain involved in mood regulation
- Gradual increases in hormone concentrations within the cortisol stress system (the hypothalamic-pituitary-adrenal axis) \rightarrow overactivity been found in people with depression (Figure 2. Pathophysiology\textsuperscript{23})
Risk Factors
Pregnancy is a major psychological life event. Women who are coping with other more chronic life stressors may find the additional stress of pregnancy unmanageable. The following are risk factors for increased prevalence of depression during pregnancy:

- Life stress
- Lack of social support
- Domestic violence
- History of depression prior to pregnancy
- Maternal anxiety
- Unintended pregnancy
- Ambivalence towards the pregnancy
- Lower income
- Lower education
- Smoking
- Single status
- History of antepartum or postpartum depression
- Family history of depression
- Discontinuing or decreasing antidepressant medication

Consequences
The following are consequences of untreated depression on the mother and infant:

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal/Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Impaired judgment leading to noncompliance with prenatal care</td>
<td>• Miscarriage</td>
</tr>
<tr>
<td>• Self-medication with tobacco, alcohol, and drugs</td>
<td>• Preterm Delivery</td>
</tr>
<tr>
<td>• Poor appetite and poor weight gain</td>
<td>• Low birth weight</td>
</tr>
<tr>
<td>• Insomnia</td>
<td>• Neonatal behavioral syndrome</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>• Less activity and attentiveness</td>
</tr>
<tr>
<td>• Worsening of depression</td>
<td>• Fewer facial expressions</td>
</tr>
<tr>
<td>• Impaired maternal-infant bonding</td>
<td>• Postpartum depression</td>
</tr>
<tr>
<td>• Postpartum depression</td>
<td>• Suicidal ideation and suicide</td>
</tr>
<tr>
<td>• Suicidal ideation and suicide</td>
<td>• Ambivalence towards the pregnancy</td>
</tr>
</tbody>
</table>

Treatment
The American Psychiatric Association and the American College of Obstetricians and Gynecologists report on depression and pregnancy, goals of treatment are maintaining euthymic mood in the mother throughout the pregnancy and preventing postpartum de-compensation.

- Treatments vary depending on severity of the symptoms and prior history of treatment and response:
  - Psychotherapy - suggested for the initial treatment of mild-to-moderate symptoms in the drug-naive patient who is not suicidal
  - Pharmacotherapy - suggested for women with a prior history of a good response to medications. Women with moderate-to-severe symptoms are best managed with psychotropic medications as the first line of treatment

Pharmacotherapy
- There are no antidepressant drug efficacy trials in depressed pregnant women. However, there is little reason to think that response would differ between pregnant and non-pregnant women
- In 2003, approximately 13% of women took an antidepressant at some point in pregnancy, a rate that has doubled since 1999
- All psychotropic medications cross the placenta, thus exposing the developing fetus to these drugs

Simien | 3
The potential risks of in utero exposure to antidepressant medications depend on numerous factors such as:
- Gestational age
- Duration of exposure
- Comorbid factors

Psychotropic medication selection is based upon:
- The woman's prior response to psychotropic medications
- Family history of response (especially in the drug-naïve patient)
- Side effect profile in each individual woman
- Potential adverse effects of the medication for the woman and her fetus
- Whether the woman plans to breastfeed

**Selective Serotonin reuptake Inhibitors (SSRIs)**

Since their introduction in 1988, SSRIs have been the treatment of choice in moderate to severe maternal depression during pregnancy.

- **Background:**
  - SSRIs are a class of compounds typically in the treatment of depression
  - SSRIs inhibit serotonin reuptake in the presynaptic neurons
  - The current model of SSRIs (the Monoamine Hypothesis) assumes that a lower homeostatic level of serotonin is primarily responsible for depression

- **SSRI Use & Pregnancy - SSRIs** have been associated with the following transient neonatal effects:
  - SSRI discontinuation syndrome
  - SSRI toxicity
  - SSRI side effects
  - Neonatal behavioral syndrome
  - Miscarriage
  - Stillbirth
  - Preterm birth
  - Shorter gestation
  - Low birth weight
  - **Persistent pulmonary hypertension of the newborn (PPHN)**

![SSRI Mechanism of Action](image)
PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Introduction\(^8,9\)

- Persistent pulmonary hypertension of the newborn (PPHN) is defined as the failure of the normal circulatory transition that occurs after birth
  - Pulmonary vascular resistance (PVR) remains elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways
  - This leads to severe hypoxemia that may not respond to conventional respiratory support
- The prevalence of PPHN has been estimated at 1.9 per 1000 live births
- Some degree of pulmonary hypertension complicates the course of more than 10% of all neonates with respiratory failure
- PPHN occurs primarily in term or late preterm infants ≥34 weeks gestation.
- Figure 4. Normal Fetal Circulation\(^25\)
**Diagnosis**

- The diagnosis of PPHN should be considered in any infant with severe cyanosis
  - Usually associated with tachypnea and respiratory distress
  - Respiratory distress and cyanosis typically occur within 6-12 hours of birth
- Diagnosis is made by echocardiography
  - Cardiac examination may reveal a loud, single S2 sound or a harsh systolic murmur secondary to tricuspid regurgitation

**Etiology**

PPHN can be generally characterized as one of 3 following types:

<table>
<thead>
<tr>
<th>Types of PPHN</th>
<th>Underdevelopment</th>
<th>Maladaptation</th>
<th>Maldevelopment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td>Hypoplastic vasculature</td>
<td>Constricted pulmonary vasculature</td>
<td>Normal lung parenchyma and remodeled pulmonary vasculature</td>
</tr>
</tbody>
</table>
| **Differential Diagnosis** | • Congenital diaphragmatic hernia (10%) | • Lung parenchymal diseases:  
  ➢ Meconium Aspiration Syndrome (41%)  
  ➢ Pneumonia (14%)  
  ➢ Respiratory Distress Syndrome (13%) | • Idiopathic (17%)
  ➢ **SSRI USE**
  ➢ Perinatal depression
  ➢ Lung parenchymal diseases
  ➢ Bacterial infections
  ➢ NSAIDS |

**Risk Factors**

Risk factors associated with PPHN include:

- Maternal obesity
- Maternal black or Asian race
- Smoking
- Diabetes
- Asthma
- Cesarean delivery
- Late preterm or postterm birth
- Large for gestational age
**Pathophysiology – PPHN & SSRIs**

Animal studies have shown that a causal relationship between SSRI exposure and PPHN is biologically plausible.

- For example, accumulation of serotonin in the rat fetal lung may lead to vasoconstriction and proliferation of pulmonary smooth muscle cells

**Treatment**

- Per American Academy of Pediatrics treatment is directed toward promoting a progressive decline in the ratio of PVR to SVR, maintain adequate tissue oxygenation until PVR falls
- The management of PPHN is largely supportive:
  - Supplemental oxygen
  - Mechanical ventilation
  - Maintenance of adequate circulatory
  - Inhaled nitric oxide (iNO)
  - Extracorporeal membrane oxygenation (ECMO)
- Specific treatment is provided for any associated parenchymal lung disease.

**Outcome**

- Survivors of severe PPHN and/or ECMO treatment are at increased risk of developmental delay, motor disability, and hearing deficits
- As recently as the late 20th century, the mortality rate for PPHN was nearly 40%, and the prevalence of major neurologic disability was 15-60%
- The introduction of ECMO and other new therapies has had a major effect on reducing the mortality rate associated with PPHN
- Monitoring - Assessment should be performed through infancy at 6 to 12 month intervals, and longer if abnormalities are present. Hearing should be tested prior to hospital discharge and at 18 to 24 months

**THE CONTROVERSY**

- With the rise in maternal use of SSRIs, there has been a growing awareness of potential adverse effects of SSRI exposure in the offspring
- The U.S. Food and Drug Administration (FDA) initially released communication regarding potential risk of PPHN in July 2006 following the results of a single study. SSRI product labeling was updated to include the risk of PPHN and SSRI use in late pregnancy
- Since 2006 there have been conflicting findings from new studies, making it unclear whether use of SSRIs during pregnancy can cause PPHN
- Objective of literature review is to evaluate risk of PPHN with SSRI use
## LITERATURE REVIEW

### CHAMBERS et al (2006) SELECTIVE SEROTONIN-REUPTAKE INHIBITORS AND RISK OF PULMONARY HYPERTENSION OF THE NEWBORN\(^{14}\)

<table>
<thead>
<tr>
<th>Objective</th>
<th>• Test the hypothesis that exposure to SSRIs during late pregnancy (after 20 weeks) is associated with an increased risk of PPHN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>• Multicenter case controlled study nested within the Birth Defects Study&lt;br&gt;• Study subjects from 97 institutions in four metropolitan areas (Boston, Philadelphia, San Diego, Toronto) were identified between 1998 and 2003</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td>• Women whose infants had PPHN&lt;br&gt;• Diagnostic criteria for PPHN:&lt;br&gt; ➢ Gestational age of more than 34 weeks&lt;br&gt; ➢ Presentation shortly after birth with severe respiratory failure&lt;br&gt; ➢ Evidence of pulmonary hypertension</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
<td>• Evidence of any cardiac anomaly except for patent ductus arteriosus, patent foramen ovale, an atrial septal defect, or a single, small, muscular ventricular septal defect</td>
</tr>
<tr>
<td><strong>Comparison Group</strong></td>
<td>• Control women and their infants, consisted of infants born after 34 weeks of gestation without malformations who were matched with patients according to the hospital in which they were born and their date of birth (±30 days)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>• Within 6 months of delivery, maternal interviews via telephone were conducted by nurses, who were blinded to the study hypothesis, regarding medication use in pregnancy and potential confounders, including demographic variables and health history</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>• Exposure to an SSRI (fluoxetine, paroxetine, sertraline) after the completion of the 20th week of gestation</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td>• Maternal education, maternal race/ethnic group, maternal pre-pregnancy BMI, maternal diabetes, smoking, alcohol intake, use of all medications after the completion of the 20th week of gestation (including NSAIDS)</td>
</tr>
<tr>
<td><strong>STATISTICAL ANALYSIS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Statistical Tests</strong></td>
<td>• Multivariate conditional logistic regression was used to estimate prevalence odds ratios (OR)&lt;br&gt;• 95% t confidence intervals (CI) for PPHN in relation to antidepressant exposure&lt;br&gt;• Risk estimates were adjusted for potential confounders</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Demographics</strong></td>
<td>• 377 infants with confirmed PPHN diagnosis&lt;br&gt; ➢ 60 preterm (born after a gestation period of &gt;34 through &lt;37 weeks)&lt;br&gt; ➢ Among infants born at term, 265 were born with a patent ductus arteriosus&lt;br&gt; ➢ Frequency of infant death up to the time of the maternal interview was 3.0%&lt;br&gt;• 836 matched controls (for a case–control ratio of 1:2.2)&lt;br&gt; ➢ Frequency of infant death up to the time of the maternal interview was 0%</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>• 14 infants with PPHN had been exposed to a SSRI, 6 control infants (adjusted OR 6.1; 95% CI 2.2 - 16.8)&lt;br&gt;• Neither the use of SSRIs before the 20th week of gestation nor the use of non-SSRI antidepressant drugs at any time during pregnancy was associated with an increased risk of PPHN&lt;br&gt;• The proportion of SSRI exposed women taking another psychoactive drug in the second half of the pregnancy was similar for mothers of patients (29%) and mothers of controls (33%)</td>
</tr>
</tbody>
</table>
Primary Endpoint

### Secondary Endpoints
- Maternal factors significantly associated with PPHN in unadjusted analyses included lower educational level, black or Asian race, higher pre-pregnancy BMI, maternal diabetes, and male infants.
- Maternal factors associated in unadjusted analyses with SSRI use in the control group included tobacco, alcohol use, maternal diabetes, a BMI of more than 27, and white race.

### Conclusion

#### Author’s Conclusion
- On the assumption that the relative risk of 6.1 for PPHN observed is true, the absolute risk among those who use SSRIs late in pregnancy is about 6 to 12 per 1000 women - about 99% of women exposed to one of these medications late in pregnancy will deliver an infant unaffected by PPHN.

#### Strengths
- Large study
- Strict diagnostic criteria used to verify cases
- Controlling for potential confounders, including maternal body-mass index, smoking, use of NSAIDs in late pregnancy, and diabetes

#### Weaknesses
- Retrospective design - telephone interviews within 6 months of delivery introduces the possibilities of inaccurate recall or recall bias
- 30% non-response rate
- Although statistically significant, results are based on a relatively small number of exposed mothers with affected infants

#### Implications
- Provided rationale for the initial Public Health Advisory in July 2006 on the risk of PPHN with SSRIs and the current SSRI product label warning.

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**Table 2. Use of SSRIs and Other Antidepressants during Pregnancy by Mothers of Infants with PPHN and Matched Controls.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definite PPHN (N=377)</th>
<th>Matched Controls (N=836)</th>
<th>Crude Matched Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal use of antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never during pregnancy</td>
<td>357 (94.7)</td>
<td>799 (95.6)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Any time during pregnancy</td>
<td>20 (5.3)</td>
<td>37 (4.4)</td>
<td>1.3 (0.7–2.2)</td>
<td>1.4 (0.8–2.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>SSRI</td>
<td>16 (4.2)</td>
<td>24 (2.9)</td>
<td>1.5 (0.8–2.9)</td>
<td>1.6 (0.8–3.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Other antidepressant</td>
<td>4 (1.1)</td>
<td>13 (1.6)</td>
<td>0.8 (0.3–2.4)</td>
<td>0.8 (0.2–2.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Maternal use of SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never during pregnancy</td>
<td>357 (94.7)</td>
<td>799 (95.6)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Before wk 20</td>
<td>6 (1.6)</td>
<td>26 (3.1)</td>
<td>0.5 (0.2–1.3)</td>
<td>0.6 (0.2–1.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>After wk 20</td>
<td>14 (3.7)</td>
<td>11 (1.3)</td>
<td>2.9 (1.3–6.5)</td>
<td>3.2 (1.3–7.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Maternal use of SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never during pregnancy</td>
<td>361 (95.8)</td>
<td>812 (97.1)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Before wk 20</td>
<td>2 (0.5)</td>
<td>18 (2.2)</td>
<td>0.3 (0.1–1.1)</td>
<td>0.3 (0.1–1.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>After wk 20†</td>
<td>14 (3.7)</td>
<td>6 (0.7)</td>
<td>5.1 (1.9–13.3)</td>
<td>6.1 (2.2–16.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3 (0.8)</td>
<td>4 (0.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>7 (1.9)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>4 (1.1)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PPHN denotes persistent pulmonary hypertension of the newborn, CI confidence interval, and SSRI selective serotonin-reuptake inhibitor.
†Odds ratios have been adjusted for maternal race or ethnic group, prepregnancy body-mass index, and diabetes. Further adjustment for other factors (e.g., smoking, alcohol intake, and use of NSAIDs after week 20) did not substantially change the results.
‡The P values refer to adjusted comparisons.
§All mothers who reported the use of citalopram discontinued the medication before the second half of gestation.
**Objective**

- Verify the observation of an association between maternal use of SSRI and PPHN

**METHODS**

**Study Design**

- Population based retrospective cohort study
- Subjects from Swedish Medical Birth Register

**Inclusion Criteria**

- Swedish women who gave birth between 1997-2005, used maternal health service, and attended first antenatal care visit

**Intervention**

- Review of data gathered from the Swedish Medical Birth Register
  - Infants were identified from discharge diagnoses using ICD-10 code
  - Maternal exposure to drugs from midwife interviews from first antenatal care visit, and from prescriptions from the antenatal care service
  - Other data collected included: maternal age, first parity, maternal BMI, and smoking

**Primary Endpoint**

- SSRI (fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, escitalopram) use during pregnancy and PPHN

**Secondary Endpoints**

- Year of birth, maternal age, parity, tobacco use, maternal diabetes, maternal pre-pregnancy BMI, gestational duration

**STATISTICAL ANALYSIS**

**Analyses & Statistical Tests**

- Mantel-Haenszel tests used to estimate 95% CI

**RESULTS**

**Baseline Demographics**

- 831,324 infants identified
  - 506 infants with discharge diagnosis of PPHN
  - Mothers of 7587 infants reported the use of SSRI drugs in early pregnancy

**Primary Endpoint**

- 11 women whose infants had PPHN reported using SSRI early in pregnancy, 5 of which reported also using SSRI late in pregnancy
- Adjusting variables and year of birth, an association between SSRI use in early pregnancy and PPHN for:
  - ALL infants identified (RR of 2.01, 95% CI 1.0-3.6)
  - Births after 34 completed weeks (RR of 2.38, 95% CI 1.19-4.25)
  - Births after 34 completed weeks - WITH known exposure also late in pregnancy (RR 3.57, 95%CI 1.16-8.33)

**Table 1. Risk for an infant to have PPHN at different gestational duration when the mother had used SSRI during pregnancy**

<table>
<thead>
<tr>
<th>Gestational Duration</th>
<th>Total</th>
<th>Exposed to SSRI With PPHN</th>
<th>Observed</th>
<th>Expected</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed in early Pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Infants</td>
<td>7587</td>
<td></td>
<td>11</td>
<td>5.47</td>
<td>2.01</td>
<td>1.00-3.60</td>
</tr>
<tr>
<td>≥34 weeks</td>
<td>7431</td>
<td></td>
<td>11</td>
<td>4.63</td>
<td>2.38</td>
<td>1.19-4.25</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>6993</td>
<td></td>
<td>9</td>
<td>3.81</td>
<td>2.36</td>
<td>1.08-4.78</td>
</tr>
<tr>
<td>Exposed in early Pregnancy WITH known exposure also late in pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Infants</td>
<td>2414</td>
<td></td>
<td>5</td>
<td>1.72</td>
<td>2.91</td>
<td>0.94-6.78</td>
</tr>
<tr>
<td>≥34 weeks</td>
<td>2350</td>
<td></td>
<td>5</td>
<td>1.4</td>
<td>3.57</td>
<td>1.16-8.33</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>2192</td>
<td></td>
<td>4</td>
<td>1.24</td>
<td>3.70</td>
<td>1.01-9.48</td>
</tr>
</tbody>
</table>

**Secondary Endpoints**

- Putative maternal factors with increase risk for PPHN:
  - increasing maternal age, first birth, smoking (not significant), high BMIs, short gestation
CONCLUSION

Author’s Conclusion

• This study supports the association between maternal use of SSRI and an increased risk for PPHN
• Prenatal exposure to an SSRI was associated with a 0.15% (1.5 per 1000) risk of PPHN

Strengths

• Large study
• Controlling for potential confounders

Weaknesses

• Incomplete detection of exposures
• Cases identified through coding only
• Very low incidence of PPHN in population
• Information on drug exposure late in pregnancy was not available
• No exclusion criteria

WICHMAN et al (2009) CONGENITAL HEART DISEASE ASSOCIATED WITH SELECTIVE SEROTONIN REUPTAKE INHIBITOR USE DURING PREGNANCY

Objective

• To determine the risk of congenital cardiac abnormalities associated with use of SSRIs during pregnancy

METHODS

Study Design

• Retrospective cohort study
• Study subjects from all obstetric deliveries at Mayo Clinic’s site in Rochester, MN from January 1, 1993 to July 15, 2005

Inclusion criteria

• Pregnant women with a documented medication list during their pregnancy that included an SSRI or who were given at least 1 SSRI prescription during their pregnancy

Intervention

• Review medical records of the newborns exposed to SSRIs during pregnancy

Primary Endpoint

• Newborns exposed to SSRIs during pregnancy, positive for congenital heart disease (CHD), ventricular septal defects (VSD), and PPHN

STATISTICAL ANALYSIS

Analyses & Statistical Tests

• Characteristics of the study population were summarized using total number and percentages or medians and inter-quartile ranges, as appropriate
• Kruskal-Wallis tests, Wilcoxon rank sum tests, Fisher exact tests
• All tests were 2-sided, and P<.05 was considered statistically significant

RESULTS

Baseline Demographics

• 25,214 deliveries identified
• A total of 808 (3.2%) were exposed to an SSRI at some point during the antenatal period:

<table>
<thead>
<tr>
<th>TABLE 1. SSRI Use During Pregnancy in 808 Patients, by Typea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Escitalopram</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>More than 1 SSRI</td>
</tr>
</tbody>
</table>

aData are number (percentage) of patients. SSRI = selective serotonin reuptake inhibitor.
Primary Endpoint

- Total of 208 newborns (0.8%) were diagnosed as having CHD (P =.23)
  - 3 newborns (0.4%) exposed to a SSRI
  - 205 newborns not exposed to a SSRI
- Total 16 newborns (0.07%) were diagnosed as having PPHN (P>.99)
  - 0 newborns exposed to a SSRI

<table>
<thead>
<tr>
<th>CHD outcome</th>
<th>SSRI use (n=808)</th>
<th>No SSRI use (n=24,406)</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPHN</td>
<td>0 (0.0)</td>
<td>16 (0.07)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>VSD</td>
<td>0 (0.0)</td>
<td>24 (0.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.4)</td>
<td>181 (0.7)</td>
<td>.29</td>
</tr>
<tr>
<td>Total</td>
<td>3 (0.4)</td>
<td>205 (0.8)</td>
<td>.23</td>
</tr>
</tbody>
</table>

a CHD = congenital heart disease; PPHN = persistent pulmonary hypertension of the newborn; SSRI = selective serotonin reuptake inhibitor; VSD = ventricular septal defect.

b Fisher exact test.
c Twenty-four had isolated VSDs, and 50 had VSDs with some other condition (included in “other” CHD category).

Other

- Dose and timing of SSRI use during pregnancy (n=694)
  - 545 (78.5%) of the exposures occurred at conception
  - 477 (87.5%) continued taking the SSRI after learning of their pregnancy
  - The median doses of several SSRIs (citalopram, venlafaxine, fluoxetine, sertraline) were significantly lower when prescribed during the second and third trimesters compared with the doses given before conception

CONCLUSION

Author’s Conclusion

- No association between CHD or PPHN and SSRI use during pregnancy
- Statistically significant difference in the doses of SSRIs prescribed during the second and third trimesters compared with the doses used before conception may be attributable to the hesitancy of physicians to prescribe SSRIs during pregnancy

Strengths

- Drug exposure information based on obstetrics database - no recall bias
- Reviewed timing of SSRI use during pregnancy - conception, discontinuation, first trimester, second trimester, third trimester
- Reviewed specific SSRI and dose used during pregnancy

Weaknesses

- Underpowered to detect small effects
- No review of demographic or clinical information, including use of other prescription or nonprescription drugs, tobacco use, or alcohol use that may affect fetal outcomes
- Unable to determine adherence to prescribed SSRI therapy during pregnancy - data taken from physician prescriptions rather than pharmacy records
- Did not review the actual amount of time the fetus was exposed to an SSRI - timing refers to when first exposed to SSRI

### Objective
- Determine the prevalence of PPHN among infants whose mothers were exposed to antidepressants in the third trimester of pregnancy

### METHODS

**Study Design**
- Multicenter retrospective cohort
- Subjects from administrative databases of four health plans participating in the HMO Research Network Center for Education and Research on Therapeutics from 1 January 1996 through 31 December 2000

**Inclusion criteria**
- Female members older than 15 years of age admitted to a hospital for delivery of an infant and were continuously enrolled in the health plan with prescription drug coverage for 1 year prior to the admission

**Comparison Group**
- Full-term or near-term infants whose mothers did not receive an antidepressant during the third trimester (matched 1:1 by health plan, maternal age [5-year age group], and year of admission for delivery)

**Intervention**
- Review of data collected from administrative databases
- Data collected included:
  - Maternal age, health plan enrollment status, prescription drug dispensing, preterm delivery or birth, maternal diabetes, asthma, cesarean section, inpatient & outpatient diagnoses and procedures indicative of PPHN documented first 14 days of life through the use ICD-9-CM, CPT, ICD-9, and HCPCS codes
  - For exposed and unexposed infants with PPHN diagnosis or procedure code full text hospital records reviewed to confirm diagnosis using structured data collection instrument and trained medical record reviewers blinded to drug exposure status and PPHN diagnosis

**Primary Endpoint**
- Full-term or near-term infants whose mothers received an antidepressant during the 3\textsuperscript{rd} trimester of pregnancy and PPHN (antidepressants identified as SSRIs, TCAs, other misc.)

**Secondary Endpoints**
- Maternal diabetes, asthma, cesarean section

### STATISTICAL ANALYSIS

**Analyses Statistical Test**
- Poisson distribution used to calculate RR

### RESULTS

**Baseline Demographics**
- 1104 infants exposed to antidepressants in the third trimester
  - 55% received an SSRI in the 1\textsuperscript{st} trimester
  - 59% received an SSRI in the 2\textsuperscript{nd} trimester
  - 85% received an SSRI in the 3\textsuperscript{rd} trimester
- Matched sample of 1104 unexposed infants

**Primary Endpoint**
- 5 infants were classified as having PPHN
  - 2 infants exposed to a SSRI in the 3\textsuperscript{rd} trimester (and 1\textsuperscript{st} & 2\textsuperscript{nd} trimester)
    - Prevalence of PPHN among infants whose mothers were exposed to SSRIs in the 3rd trimester was 2.14 per 1000 (95%CI 0.26 - 7.74)
    - Prevalence of PPHN among infants whose mothers were not exposed was 2.72 per 1000 (95%CI 0.56 - 7.93)

**Secondary Endpoints**
- Maternal diabetes and asthma more common among exposed group (p=0.0001)
CONCLUSION

<table>
<thead>
<tr>
<th>Author’s Conclusion</th>
<th>No association between SSRI use in late pregnancy and PPHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strengths</td>
<td>Database use - avoid recall bias</td>
</tr>
<tr>
<td></td>
<td>Hospital chart review - able to confirm PPHN diagnosis</td>
</tr>
<tr>
<td>Weaknesses</td>
<td>Small number of confirmed cases of PPHN</td>
</tr>
<tr>
<td></td>
<td>Some cases of PPHN may have not been identified (no ICD-9 code available)</td>
</tr>
</tbody>
</table>


Objective

- Determine if maternal use of SSRIs in the second half of pregnancy is associated with PPHN

METHODS

Study Design

- Case controlled study (1:6 ratio)
- Infants delivered at Madigan Army Medical Center from 2003 through 2009

Inclusion criteria

- Neonates born at ≥34 weeks gestation and verified to have PPHN by experienced neonatologist

Exclusion Criteria

- Neonates with congenital anomalies known to cause pulmonary hypertension (diaphragmatic hernia, meconium aspiration syndrome, sepsis)

Comparison Group

- For each case, the next 6 births occurring at the same gestational age in weeks were identified from the hospital’s delivery log

Intervention

- Review of electronic medical records (EMR) of all infants diagnosed with PPHN and control patients.
  - Data collected included: maternal age, parity, body mass index, maternal diabetes, chorioamnionitis, fetal gender, tobacco use, mode of delivery, SSRI medications after 20 weeks gestation (prescription medication captured in 3 ways: computerized database of filled prescriptions, review of outpatient EMR, review of inpatient EMR at time of delivery)

Primary Endpoint

- SSRI use after 20 weeks gestation and PPHN

Secondary Endpoints

- Mode of delivery, maternal disease, body mass index, tobacco use, fetal gender, maternal age, and parity

STATISTICAL ANALYSIS

Analyses & Statistical Tests

- Chi-square or Fisher exact tests used to calculate ORs
- Cochran Mantel-Haenzel technique used to calculate adjusted ORs
- Poisson distribution used to calculate the CIs for the late exposure to SSRIs
- Statistical significance was set at an α level of 0.05

RESULTS

Baseline Demographics

- Total of 11,923 births
- 20 (0.17%) cases of PPHN

Primary Endpoint

- SSRIs use in the second half of pregnancy was identified in:
  - None of the study cases
  - 5% of the controls (OR = 0, CI 0 - 3)

Secondary Endpoints

- Mode of delivery was the only factor found to be associated with PPHN:
  - Cesarean delivery prior to the onset of labor increased the risk for PPHN (OR = 4.9, CI 1.7 - 14.0) - results remained statistically significant after controlling for other variables
Current Data
- Data are limited and conflicting on whether or not exposure to any SSRI may increase the risk of PPHN
- In these reports, the following limitations make it uncertain whether or not antenatal SSRI exposure has a direct, causal and independent negative effect on offspring:
  - Confounding variables poorly controlled
    - Examples: severity of maternal depression, comorbid psychiatric disorders, congenital anomalies known to cause pulmonary hypertension
  - Study results based upon pooled variety of SSRIs
    - SSRIs vary in potency, receptor selectivity, and pharmacokinetic properties, which alter their impact on an exposed infant
  - Poor study design
    - Lack of validation of fetal exposure, non-standardized neonatal assessment, non-standardized diagnostic criteria, small sample sizes

FDA Statement
- The FDA has concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN
  - The FDA is advising health care professionals not to alter their current clinical practice of treating depression during pregnancy and to report any adverse events to the FDA MedWatch

Conclusion
- Does SSRI use in pregnancy increase risk of PPHN? NO
- Untreated maternal depression poses significant risks to both the mother and child
  - These risks often outweigh the risks associated with pharmacotherapy, such as SSRI use
  - There is no evidence that tapering or discontinuing antidepressant medication near term is necessary, safe, or effective in terms of preventing PPHN
- Changes in pharmacologic treatment of maternal depression should be considered if an independent association of SSRIs and PPHN needs to be confirmed
  - Future studies are needed that eliminate poor study designs, confounding variables, issues with certainty of PPHN, the inability to confirm fetal exposure to the drug, and the inability to separate the effects of maternal SSRI use from those related to depression
<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>DEFINITION</th>
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<th>DEFINITION</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
<td>ICD-9-CM</td>
<td>International Classification of Diseases -9- Clinical Modification</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
<td>iNO</td>
<td>Inhaled nitric oxide</td>
</tr>
<tr>
<td>CHD</td>
<td>Congenital heart disease</td>
<td>NSAIDS</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>EMR</td>
<td>Electronic medical records</td>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>CPT</td>
<td>Current procedural terminology</td>
<td>PPHN</td>
<td>Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>DSM IV</td>
<td>Diagnostic and statistical manual of mental disorders</td>
<td>RR</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>CRF</td>
<td>Corticotropin-releasing hormone</td>
<td>TCA</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>HCPCS</td>
<td>Healthcare common procedure coding system</td>
<td>VSD</td>
<td>Ventricular septal defects</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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</table>

REFERENCES


24. www.nature.com, accessed February 2012

25. www.apsu.edu, accessed February 2012