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Selective Serotonin Re-uptake Inhibitors (SSRIs) Exposure in Late Pregnancy and Incidence of Persistent Pulmonary Hypertension of the Newborn (PPHN)

Robert Parker
Pacific University

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Abstract
Background: Persistent pulmonary hypertension of the newborn (PPHN) is a rare but serious and potentially fatal clinical condition. Recent reports have suggested a possible association with the development of PPHN in the neonate, to mothers who have been exposed in the later stages of pregnancy to selective serotonin re-uptake inhibitors (SSRI), an antidepressant medication. This review will investigate the most recent literature to determine the prevalence of PPHN among mothers exposed to SSRIs in late pregnancy.

Methods: A systematic review of the literature published in the previous five years was conducted on the MEDLINE, CINAHL, and ISI World of Science databases using the keywords PPHN, SSRI, and pregnancy. Articles that examined outcomes of PPHN with SSRI exposure in pregnancy after 20 gestational weeks were selected. Research that focused on antidepressant use other than SSRIs or outcomes with early exposure during pregnancy was excluded.

Results: Three articles that investigated the effects of SSRI exposure in late pregnancy and PPHN were analyzed for significant results. Two of the three articles agreed that there is an almost six fold increase in PPHN in infants exposed to SSRIs later in pregnancy. One study found no significant difference in the prevalence of PPHN and SSRI use in the third trimester of pregnancy.

Conclusion: The data reviewed suggests that there is a possible connection with SSRI exposure in late pregnancy and the development of PPHN in infants. However, the data at this time are limited and not conclusive. The information gathered in this systematic review should be considered in the decision to initiate, continue, or discontinue an SSRI during pregnancy.

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First Advisor
James Ferguson PA-C, MPH

Second Advisor
Anjanette Sommers MS, PAC

Third Advisor
Rob Rosenow PharmD, OD

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Selective Serotonin Re-uptake Inhibitors (SSRIs) Exposure in Late Pregnancy and Incidence of Persistent Pulmonary Hypertension of the Newborn (PPHN)

Robert Parker

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 14, 2010

Faculty Advisor: Prof. James Ferguson
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Robbie Parker was born in Ogden, Utah; the fourth of five children in his family, however, the only one that was planned. His birth was initially a disappointment after being born as the number two baby on New Years Day. Meaning his parents received no special presents and no extra tax break after his arrival. Despite his early failures Robbie has grown up happy with who he is and what he has accomplished.

Robbie then spent the next ten years of his life growing up in Arlington, TX where he became an avid fan of Texas Rangers Baseball and real Texas BBQ, both of which he has found fail to provide any genuine long-term satisfaction but are absolutely wonderful in short spurts. Upon his families return to Utah he developed a love for the mountains and fly-fishing. At age 16, after a series of unfortunate events for someone else, Robbie was given a job as the mascot “Oggie” a velociraptor, for the minor league baseball team in town. After realizing this would be as close as he would ever get to the major leagues, he decided that his life-long dream of having his own baseball card was technically fulfilled and therefore sought out a new direction in life. He was awarded a scholarship to be the mascot “Waldo the Wildcat” at Weber State University and received his Bachelors of Science in Respiratory Therapy. At that time Robbie found his new dream when he accepted the first legitimate job of his life, as a respiratory therapist in a newborn intensive care unit.

Robbie attributes any success he has had in life to simple dumb luck or for merely showing up at the right place at the right time. Except for what he considers his greatest success, his wife and daughters. Currently, he is married to the most beautiful and intriguing woman in the history of the world. They have three absolutely wonderful daughters, Emilie (4), Madeline (2) and Samantha (1). His life and this world are a much better place because of them. After graduation he will fulfill his goal of working in a newborn intensive care unit and cannot wait to start a new adventure with his sweetheart and precious children.
Abstract

**Background:** Persistent pulmonary hypertension of the newborn (PPHN) is a rare but serious and potentially fatal clinical condition. Recent reports have suggested a possible association with the development of PPHN in the neonate, to mothers who have been exposed in the later stages of pregnancy to selective serotonin re-uptake inhibitors (SSRI), an antidepressant medication. This review will investigate the most recent literature to determine the prevalence of PPHN among mothers exposed to SSRIs in late pregnancy.

**Methods:** A systematic review of the literature published in the previous five years was conducted on the MEDLINE, CINAHL, and ISI World of Science databases using the keywords PPHN, SSRI, and pregnancy. Articles that examined outcomes of PPHN with SSRI exposure in pregnancy after 20 gestational weeks were selected. Research that focused on antidepressant use other than SSRIs or outcomes with early exposure during pregnancy was excluded.

**Results:** Three articles that investigated the effects of SSRI exposure in late pregnancy and PPHN were analyzed for significant results. Two of the three articles agreed that there is an almost six fold increase in PPHN in infants exposed to SSRIs later in pregnancy. One study found no significant difference in the prevalence of PPHN and SSRI use in the third trimester of pregnancy.

**Conclusion:** The data reviewed suggests that there is a possible connection with SSRI exposure in late pregnancy and the development of PPHN in infants. However, the data at this time are limited and not conclusive. The information gathered in this systematic review should be considered in the decision to initiate, continue, or discontinue an SSRI during pregnancy.

**Keywords:** PPHN, SSRI, pregnancy
Acknowledgements

To my wife, Alissa and my three wonderful daughters. You are my reasons for everything I do and I could not do anything without you. I humbly thank you for your love and support!!
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List of Abbreviations

PPHN.................................................................Persistant Pulmonary Hypertension of the Newborn
SSRI.................................................................Selective Seratonin Re-uptake Inhibitor
BACKGROUND

Overview

Persistent pulmonary hypertension of the newborn (PPHN) is a rare but serious and sometimes fatal neonatal complication. PPHN is a condition characterized when the pulmonary vasculature fails to relax after birth, leading to a decrease in pulmonary blood flow and shunting of un oxygenated blood to the systemic circulation.\(^1\),\(^2\) PPHN occurs in an estimated 1-2 per 1000 live births and is more commonly found in full-term or near-term infants than pre-term infants.\(^2\)

A number of clinical conditions, including meconium aspiration syndrome, pneumonia, sepsis, respiratory distress syndrome, non-vertex presentation, post maturity, maternal diabetes, and cesarean section, are associated with PPHN.\(^2\),\(^3\) Possible physiological mechanisms leading to the development of PPHN include decreased production or responsiveness to vasodilators such as nitric oxide; increased production or responsiveness to vasoconstrictors such as endothelin; or changes in production or responsiveness to both vasodilators and vasoconstrictors.\(^4\) On pathological study, infants with PPHN are found to have congenital pulmonary vascular remodeling involving increased muscularization of the pulmonary arterioles.\(^5\)

These findings suggest that prenatal exposures can contribute to the pathogenesis of PPHN.\(^5\)

The results of a previous small cohort study conducted by a teratogen-information service generated the hypothesis that maternal use of selective serotonin re-uptake inhibitors (SSRIs) in late pregnancy may be a risk factor for PPHN.\(^6\) Among 174 infants born to women who used a specific SSRI, fluoxetine, for some portion of their pregnancies, two of the 73 babies that were exposed to fluoxetine up to the time of delivery had PPHN, as compared with zero of the 101 exposed only early in
Another recent study suggested an association between maternal use of SSRIs and PPHN in infants born after 34 gestational weeks. This study performed by Chambers et al reported a six-fold increase risk of PPHN associated with maternal use of SSRIs in late pregnancy.¹

The research done by Chambers et al is significant due to the substantial increase over the last 10 years in SSRI use during pregnancy.⁷ Approximately 4 million live births occur in the United States each year, and about 92,000 of these infants are prenatally exposed to SSRIs.⁸ SSRIs are the first-line pharmacotherapy for depression, and amounts for 77.5% of antidepressant use during pregnancy.⁸ According to one report almost three percent of all infants have been exposed to SSRIs through the end of pregnancy.⁸ Since Chambers et al was published in 2006, other studies⁷,⁹,¹⁰ have been performed testing the validity of their results.

**Purpose of Study**

The purpose of this work is to systematically review the most recent clinical research in the use of SSRIs during late pregnancy and the reported increased correlation of neonates developing PPHN. Expectant mothers are required to make decisions that impact both maternal and fetal health. Pregnant women faced with this situation must balance the most accurate information available with their particular circumstances to aide them in making the most correct decision.

**METHODS**

**Search Strategies**

A search of the literature published in the previous five years was conducted on the MEDLINE, CINAHL, and ISI World of Science databases using the following search terms: PPHN, SSRI, pregnancy. Subsidiary MeSH terms were selected where appropriate and permitted by the search
engine (i.e.- “persistent fetal circulation of the newborn” to PPHN). Consequently an examination of bibliographic entries in retrieved works provided additional sources for consideration.

This systematic review analyzed information from studies that contribute to the understanding of SSRI use in late pregnancy and particularly to its possible association with PPHN. Only studies published in the last five years with emphasis on continued or onset SSRI exposure after 20 weeks gestation to those with no exposure and outcomes of babies born after 34 weeks gestation were reviewed. Retrospective cohort and case-controlled studies were included. No randomized control trials were found in relation to this topic.

Inclusions/Exclusions

The search was limited to English language publications, expectant mothers, and neonatal outcomes. Articles that focused on antidepressants other than SSRIs, SSRIs used in early pregnancy and discontinued, depression in pregnancy or neonatal outcomes other than PPHN were excluded.

A relative score representing quality and validity was then given to each article using an original process (see Table 1). Higher scores were awarded to those studies with large population sizes, prospective exposure information, and quality of methods used to acquire information. Lower scores were awarded to studies with small population sizes, use of retrospective maternal interviews, and inability to satisfactorily reduce confounding factors. Studies were not included or excluded based solely on their score.

RESULTS

After these exclusions, three articles professed to compare SSRI use in late pregnancy and PPHN (see Table 2). These articles reviewed for the purpose of this work specifically assessed the possible relationship between SSRI exposure in late pregnancy and PPHN in neonates born after 34
weeks gestation. Chambers et al\textsuperscript{5} performed a follow up study after the authors’ previous article generated the hypothesis that maternal use of SSRIs in late pregnancy may be a risk factor for PPHN.\textsuperscript{5,6} However, the result of this study has lead other researchers to conduct their own independent studies in order to authenticate the observation of a potential connection between SSRI exposure in late pregnancy and PPHN.

A retrospective case control study performed by Chambers et al in 2006, published in The New England Journal of Medicine, enrolled 637 infants with possible PPHN. The diagnosis was then confirmed in 377 of the infants after certain inclusion/exclusion criteria were met upon review of the medical records. These 377 patients were then matched with 836 control patients that did not have exposure to SSRIs. The control group consisted of infants born after 34 weeks gestation without malformations who were matched with patients according to the hospital in which they were born and their date of birth (+/- 30 days). Within six months of delivery, trained nurses, unaware of the study hypothesis, performed telephone interviews with the mothers in both the control and study groups.\textsuperscript{5}

Chambers et al reported that the crude risk of PPHN associated with the use of any antidepressant at any time in pregnancy was not significantly elevated (odds ratio (OR), 1.3; 95% confidence interval (CI), 0.7 to 2.2), nor was the use of SSRIs alone at any time in pregnancy significantly associated with PPHN (OR, 1.5; 95% CI, 0.8 to 2.9). However, when the comparison was stratified according to the timing of exposure in pregnancy, use of any antidepressant after the 20\textsuperscript{th} week of gestation was significantly associated with PPHN (OR, 2.9; 95% CI, 1.3 to 6.5). Further analysis demonstrated that this association was entirely attributable to the subgroup of infants with late exposure to SSRIs (OR for SSRI use after 20\textsuperscript{th} week of gestation relative to no use in the pregnancy, 5.1; 95% CI, 1.9 to 13.3). There was no increased risk of PPHN when SSRI use was restricted to the first half of the pregnancy (OR, 0.3; 95% CI, 0.1 to 1.1).\textsuperscript{5}

Further analysis showed that 12 of the 14 mothers with late SSRI exposure whose infants had PPHN continued use of their medication into at least the eighth month of pregnancy. Post hoc analysis
using a cutoff point of 26 weeks gestation yielded identical results (adjusted odds ratio, 6.1; 95 percent confidence interval, 2.2 to 16.8).\textsuperscript{5}

In contrast another retrospective case control study performed by Andrade et al published in Pharmacoepidemiology and Drug Safety in 2009 found no association between SSRI use in late pregnancy and PPHN. The authors randomly matched 1104 patients who were not exposed to antidepressants with 1104 women who had received an antidepressant in the third trimester. The vast majority of women whose infants were included in the exposed group (85%) received an SSRI in the third trimester. This study used automated pharmacy records to identify medication exposures. The researchers then reviewed medical charts from 1 January 1996 to 31 December 2000 using expert reviewers looking for inpatient diagnosis or procedure codes of interest with PPHN. A total of five cases of PPHN were classified by the expert reviewers as having ‘possible’ PPHN. Two of the cases were among infants exposed to antidepressants in the third trimester and three were among infants unexposed to antidepressants. The two exposed cases were exposed to SSRIs in all trimesters of pregnancy.\textsuperscript{7}

The prevalence of PPHN among infants whose mothers were exposed to any antidepressant in the third trimester was 1.81 per 1000 infants (95% CI 0.22, 6.54) overall. Among those infants whose mothers were exposed to SSRIs in the third trimester, the prevalence was 2.14 per 1000 (95% CI 0.26, 7.74), while the prevalence of PPHN among infants whose mothers were not exposed to antidepressants was 2.72 per 1000 (95% CI 0.56, 7.93). The prevalence ratio for the association between PPHN and antidepressant use was 0.67 (95% CI 0.06, 5.82). The data generated from this study was unable to find an increased risk of PPHN with maternal use of SSRIs in the third trimester.\textsuperscript{7}

Swedish researchers Källén and Olausson gathered information from the Swedish Medical Birth Register for the years 1997-2005. Practically all Swedish women who give birth have attended the free maternal health service and make their first visit usually before gestational week 12. At this visit, the women are interviewed by a midwife and the answers are recorded in a standardized form,
used all over Sweden. Infants born to women who had used SSRI drugs during pregnancy in 1997-2005 were studied and compared with all other infants recorded in the Medical Birth Register (n= 831 324). Identification of infants with PPHN was made from neonatal diagnoses, coded in the modified ICD-10 (International Statistical Classification of Diseases and Related Health Problems) code P293B which specifies PPHN and has been used in Sweden since 1997 when ICD-10 was introduced.9

A total of 506 infants were identified with a discharge diagnosis of PPHN among the 831 324 born. When all cases were analyzed, an increased risk for PPHN was seen among the SSRI-exposed infants. The risk was slightly higher when the analysis was restricted to infants who had been exposed to SSRI in late pregnancy when compared with early pregnancy (Risk ratio (RR) 2.91; 95% CI, 0.94 to 6.78 with late exposure vs. RR, 2.01; 95% CI, 1.00 to 3.60 with early exposure). When the analysis was made on infants exposed in late pregnancy, slightly higher risk estimates were seen, statistically significant when the analysis was restricted to infants born after 34 completed gestational weeks (RR, 3.57; CI, 95% 1.16 to 8.33 late exposure vs. RR, 2.38; CI, 95% 1.19 to 4.25 early exposure).9

**DISCUSSION**

**Review**

After careful investigation of the recent literature on the topic, there remain conflicting answers about the risk of SSRI use in late pregnancy and its association with PPHN. Of the three articles assessed for the purpose of this review Chambers et al and Källén and Olausson agreed that there appears to be an increased risk with exposure of SSRIs in late pregnancy and PPHN.5, 9 The study performed by Andrade et al was unable to find any increased risk.7 Källén and Olausson’s work was unique in that although it was retrospective in nature it had an advantage that the exposure information was prospective and not based on retrospective inquiries.9 Overall the studies5, 9 that agreed on the
increased risk associated with SSRI use and PPHN were more complete and thorough than Andrade et al. Both Chambers et al and Källén and Olausson had a larger population of children with PPHN to study. They were able to limit their confounders, and their inclusion criteria were more precise than that of Andrade et al.

**Study Limitations**

The articles selected for review demonstrate different research methods and accordingly vary in their quality. Investigating the potential effect of a certain class of medication on pregnant women and unborn children has ethical considerations that prevent randomized control trials and therefore information on the specific topic is necessarily limited. Therefore, retrospective population, cohort, and case-control matched studies supply the totality of information available on the subject.

Both Chambers et al and Andrade et al searched medical records for information to identify potential cases based on certain diagnostic criteria.\(^5\)\(^,\)\(^7\) Although both studies were published recently, 2006 and 2009 respectively, during the study period chosen by the authors, no specific ICD-9 code was available for documentation of PPHN.\(^5\)\(^,\)\(^7\) This means that researches were forced to rely on an extensive search through admission/discharge records, complicated medical charts both neonatal and maternal, and neonatal intensive care logbooks to extrapolate specific information regarding depression, SSRI use, and PPHN that would meet each authors detailed criteria for inclusion into the study.\(^5\)\(^,\)\(^7\) This exhaustive search through complicated data suggests that some cases of PPHN may have been undetected in the study population.\(^7\) Andrade et al also note in their paper that the length of gestation was not available in the administrative databases and therefore they assumed a 270 day gestational period.\(^7\) Although their study intended to include only full-term or near-term infants (>34 weeks gestation) their assumption may have permitted some pre-term infants into their results.\(^7\) The use of maternal interviews performed up to six months after delivery by Chambers et al introduces the notion of recall bias into their results.
Given that PPHN is a rare condition in the general population it is difficult to design a study with an extremely large number of babies that are affected by PPHN. Andrade et al had only five cases of PPHN out of 2208 enrolled in their study. Chambers et al had 637 infants with possible PPHN but could only confirm 377 cases. Källén and Olausson needed over 830 000 babies born to find 506 infants with PPHN. This natural limitation restricts the amount of research that can be done with the relationship between SSRIs and PPHN.

**Confounders**

Confounding variables are another important concept in the analysis of all the reviewed articles. As previously mentioned there are many clinical conditions and physiological mechanisms associated with PPHN. Other maternal risk factors provide many of the confounding factors such as lower educational level, maternal age, parity, body mass index (BMI), smoking, alcohol use, use of nonsteroidal anti-inflammatory agents (NSAIDS), caesarian section, and diabetes were noted. However, information on the confounding variables was limited because the clinical question was simply based on exposure to SSRIs and development of PPHN. Only Källén and Olausson made separate analytical adjustments for four possible confounders (maternal age, parity, smoking and BMI).

All articles reviewed in this present study were simply assessing the exposure of SSRI use in late pregnancy and relationship with PPHN. None of the studies differentiated between different dosages, treatment regimens, and severity of depression among those in the exposed group.

**CONCLUSION**

After careful review of the articles mentioned in this study, there appears to be an increased risk between SSRI use in late pregnancy and PPHN. However, the data on the subject at this time is
limited and is not by any means conclusive. It should be noted that PPHN is a rare medical condition. Assuming that there is a six fold increase in the risk of SSRI use and PPHN as previously reported, the risk of having a baby with PPHN among those who use SSRIs late in pregnancy is still relatively low (about 6-12 per 1000). In other words, even assuming a six fold increased risk, about 99% of women exposed to SSRIs late in pregnancy will deliver an infant unaffected by PPHN. Despite the rarity of PPHN due to the increasing number of women who will be treated with SSRIs in their pregnancy the potential risks and benefits must be carefully considered. Further research will enable both the clinician and patient to make a more balanced assessment when confronted with the decision to safely initiate, continue, or discontinue an SSRI during pregnancy.
References


### Table 1: VRASS

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score +1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>Greater than 100 babies with PPHN in study</td>
<td>Less than 100 babies with PPHN in study</td>
</tr>
<tr>
<td>Information Gathering Method</td>
<td>Use of large conformed databases. Prospective exposure information</td>
<td>Search of medical records for possible potential cases. Use of maternal interviews.</td>
</tr>
<tr>
<td>Evident and Accurate Results</td>
<td>Clear and concise explanation of results with data sets or tables.</td>
<td>Hidden information and inability to minimize study limitations.</td>
</tr>
<tr>
<td>Study Limited Exposure to Late Pregnancy</td>
<td>Exposure after 20 weeks gestation</td>
<td>Exposure at any time during pregnancy, but results separated into early and late exposure.</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Use of precise coding specifically for PPHN</td>
<td>Based on interpretation of medical records and clinical opinions.</td>
</tr>
</tbody>
</table>

### Table 2: Reviewed Articles Matrix

<table>
<thead>
<tr>
<th>Study/Design</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome</th>
<th>RP-TASS Score (of 5)/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers <em>et al</em> (2006) Retrospective case-control</td>
<td>1213 Women and infants 377 babies with PPHN</td>
<td>SSRI in late pregnancy vs. no SSRI</td>
<td>Babies with PPHN</td>
<td>3/5. Use of maternal interviews. Initial study on clinical question</td>
</tr>
<tr>
<td>Andrade <em>et al</em> (2009) Retrospective case-control</td>
<td>2208 women and infants 5 babies with PPHN</td>
<td>SSRI in 3rd trimester of pregnancy vs. no SSRI use</td>
<td>Babies with PPHN</td>
<td>1/5. Small number of babies with PPHN. Possibility of inclusion of babies not intended in study population</td>
</tr>
<tr>
<td>Källén &amp; Olaussen (2007) Retrospective cohort</td>
<td>831 234 women 506 babies with PPHN</td>
<td>SSRI use during pregnancy vs. no SSRI use</td>
<td>Babies with PPHN</td>
<td>4/5. Use of Swedish National Birth Registrar for conformed concise information gathering.</td>
</tr>
</tbody>
</table>