



## Selective Serotonin Reuptake Inhibitors and Persistent Pulmonary Hypertension of the Newborn

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- Some studies have associated antenatal use of SSRIs with increased risk of a potentially fatal neonatal condition, persistent pulmonary hypertension of the newborn (PPHN).
- This article reviews the findings for physicians and provides plain-language talking points that can be used to answer patients' questions and guide them in making informed decisions about treatment.

**Author's note:** In this article, sertraline has been used as an example of a candidate antidepressant. This does not imply that sertraline is the preferred antidepressant for treating recurrent depressive disorder in women or for treating depression during pregnancy.

*Ms M is a 33-year-old white woman with a 6-year history of recurrent major depressive disorder. After suffering 4 episodes of severe illness at an average frequency of 1 episode per year, she finally found reasonable stability during the past 2 years with sertraline dosed at 150 mg/d. She is presently undergoing cognitive-behavioral therapy to learn how to cope with her subsyndromal mood symptoms.*

*Ms M is childless and plans to conceive. She had earlier discussed with her physician the pros and cons of discontinuing sertraline during pregnancy and had concluded that the risk-benefit analysis clearly favored continuation. Now, however, she has learned from the Internet that a new study<sup>1</sup> indicates that her medication could be associated with a doubled risk of a potentially fatal neonatal condition, persistent pulmonary hypertension of the newborn (PPHN). She is disturbed and seeks assistance in interpreting this new information.*

*Ms M has prepared a list of questions to ask:*

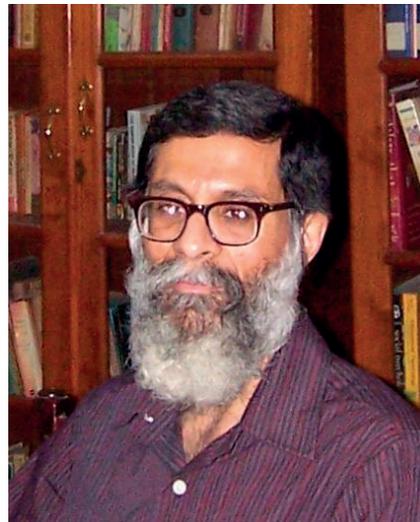
1. What is PPHN?
2. Does the new study show that sertraline causes PPHN?
3. Should I continue with sertraline, switch to a non-SSRI, or avoid antidepressants altogether?

### What Is PPHN?

PPHN is a condition in which the pulmonary vascular resistance fails to fall after birth. As a result, the ductus arteriosus remains open to ensure circulation (for this reason, PPHN is also described as *persistent fetal circulation*). Affected neonates exhibit respiratory distress and may even need mechanical ventilation; inadequate respiratory support can result in anoxia and its consequences, including brain damage. The mortality risk is about 5%–10%.<sup>2</sup>

There are many causes of persistent fetal circulation, including congenital cardiac disease, meconium aspiration (and other causes of lung injury), perinatal asphyxia, and sepsis. Selective serotonin reuptake inhibitors (SSRIs) have also been etiologically implicated with the explanatory hypothesis that serotonin can cause vasoconstriction as well as stimulate growth of the smooth muscle layer in the pulmonary arteries.<sup>3</sup>

In this column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.



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## What Is the Evidence Linking SSRIs to PPHN?

Prior to 2012, some studies have associated antenatal SSRI use with PPHN,<sup>4,5</sup> whereas other studies have failed to demonstrate a risk.<sup>6-8</sup> As a result, on December 14, 2011, the US Food and Drug Administration (FDA) issued a notification 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.”<sup>9</sup> The FDA therefore advised health care professionals “not to alter their current clinical practice of treating depression during pregnancy.” The FDA advisory suggested that health care professionals should “weigh the small potential risk of PPHN that may be associated with SSRI use in pregnancy against the substantial risks associated with undertreatment or no treatment of depression during pregnancy.” PPHN, however, is a rare condition; therefore, the small sample sizes in the literature on which the FDA<sup>9</sup> review was based limit the usefulness of the conclusions of the review.

## How Was the New Study Conducted and What Did It Find?

In 2012, Kieler et al<sup>1</sup> reexamined the association between SSRIs and PPHN in the largest study so far, using prospectively collected (thus precluding recall bias), 1996–2007 data from national health registers in Denmark, Finland, Iceland, Norway, and Sweden. The subjects in this population-based cohort study comprised all singleton births ( $n = 1,618,255$ ) after 33 weeks of gestation. Among these, 17,053 (1.1%) mothers had filled a prescription for an SSRI in early pregnancy (fluoxetine,  $n = 3,899$ ; citalopram,  $n = 6,816$ ; paroxetine,  $n = 2,293$ ; sertraline,  $n = 3,396$ ; fluvoxamine,  $n = 278$ ; escitalopram,  $n = 2,510$ ), and 11,014 (0.7%) mothers had filled a prescription for an SSRI during late pregnancy (fluoxetine,  $n = 3,315$ ; citalopram,  $n = 3,294$ ; paroxetine,  $n = 1,281$ ; sertraline,  $n = 2,843$ ; fluvoxamine,  $n = 112$ ; escitalopram,  $n = 557$ ). Early pregnancy was defined to extend from 3 months before pregnancy to the end of 8 weeks of gestation, and late pregnancy was defined to extend from the start of week 21 of gestation to the time of delivery. Overall, 1.9% of women had used an SSRI at some time during pregnancy.

Odds ratios and 95% confidence intervals were calculated after adjusting for maternal age, nonsteroidal anti-inflammatory drug and antidiabetes drug use, preeclampsia, chronic diseases during pregnancy, country of birth, birth year, level of delivery hospital, and birth order. Important findings from the study are presented in Table 1.

## TALKING WITH THE PATIENT

### “What is PPHN?”

- PPHN, or “persistent pulmonary hypertension of the newborn,” is a rare but serious condition related to blood circulation in the lungs and lung functioning at birth. PPHN has many possible causes. In a recent study, about one in a thousand newborns were affected by PPHN.
- In the womb, the baby receives oxygen from the mother through the placenta and umbilical cord. At birth, the baby begins to breathe through its own lungs, and changes take place in the circulatory system: blood starts flowing through the lungs.
- In PPHN, the lungs do not expand normally after birth and blood does not flow easily through the lungs. As a result, the baby cannot breathe normally and receives less or no oxygen from the lungs.
- Treatment of PPHN may involve intensive care and the use of a ventilator. *Among babies who have PPHN*, the risk of death is about 5% to 10%.



**Table 1. Important Findings From the Kieler et al (2012) Cohort Study<sup>1</sup> on SSRI Use During Pregnancy and the Risk of PPHN**

- SSRI-exposed infants were more likely than unexposed infants to have been born before week 37 (rates, 5.4% vs 3.8%, respectively) and were more likely to be small for gestational age (2 standard deviations below age- and sex-specific norms; rates, 3.0% vs 2.4%, respectively). These analyses were not corrected for confounders; for example, SSRI-using mothers were older, more likely to have smoked during early pregnancy, more likely to have used diabetic and NSAID medication, and more likely to have delivered by cesarean section
- There were 1,935 cases of PPHN among 1,588,140 infants with no intranatal exposure to SSRIs. Thus, the background risk of PPHN was 0.12%
- There were 32 cases of PPHN among 17,053 exposures to SSRIs in early pregnancy. Thus, the absolute risk of PPHN was 0.19% after early exposure. Relative to the background risk, this increase was of borderline significance (OR = 1.4; 95% CI, 1.0–2.0)
- After SSRI exposure in early pregnancy, the risk of PPHN with individual SSRIs was significantly elevated only for sertraline and citalopram (adjusted ORs, 1.8–1.9)
- There were 33 cases of PPHN among 11,014 exposures to SSRIs in late pregnancy. The absolute risk was significantly elevated at 0.30% (OR = 2.1; 95% CI, 1.5–3.0). Three (9.1%) of these 33 infants died
- After SSRI exposure in late pregnancy, the risk of PPHN with individual SSRIs was similar for fluoxetine, sertraline, paroxetine, and citalopram (adjusted ORs, 2.0–2.8;  $P < .05$  for each). Escitalopram and fluvoxamine were the only SSRIs for which there was no significant elevation in risk after late pregnancy exposure
- Early pregnancy exposure to antidepressants other than SSRIs (not individually listed by Kieler et al, 2012) was not associated with an increased risk of PPHN (OR = 0.6; 95% CI, 0.1–2.3). Late pregnancy exposure to antidepressants other than SSRIs was associated with an elevated risk of PPHN (3/627; 0.48%) that, however, narrowly escaped statistical significance (OR = 2.9; 95% CI, 0.9–8.9)
- There were 54,184 women with a previous psychiatric admission who had not used antidepressants during pregnancy; among their infants, there were 114 (0.21%) cases of PPHN, representing a significantly elevated risk (OR = 1.3; 95% CI, 1.0–1.6)
- The combination of a previous psychiatric admission and SSRI exposure during late pregnancy tripled the risk of PPHN (OR = 3.1; 95% CI, 1.9–4.9)
- Neither smallness for gestational age nor cesarean section delivery influenced the risk of PPHN
- In analyses in which cases of meconium aspiration were dropped and the data reanalyzed, the findings did not change

Abbreviations: NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio, PPHN = persistent pulmonary hypertension of the newborn, SSRI = selective serotonin reuptake inhibitor.

## Interpretation and Critical Viewpoint

This large study<sup>1</sup> provides strong evidence that SSRI use during pregnancy, particularly after week 20 of gestation, is associated with an increased risk of PPHN. There are several possible explanations that are not necessarily mutually exclusive:

1. SSRIs as a class of drugs may increase the risk of PPHN (because the risk was similarly elevated with all SSRIs in analyses that were adequately powered).
2. The psychiatric illness for which SSRIs are prescribed may be responsible for the elevated risk (because the risk was increased in women with a history of past psychiatric admission even when there was no use of antidepressants during the index pregnancy). Here, however, psychiatric admission is probably a marker of illness severity that predisposes to an experience or behavior that increases the risk.
3. Psychiatric medications as a class may increase the risk of PPHN (women with a previous psychiatric admission may have been taking non-antidepressant psychotropic medications).

## TALKING WITH THE PATIENT

### *“Does the new study show that sertraline causes PPHN?”*

- Sertraline is an SSRI antidepressant drug. The new study showed a statistically significantly increased risk of PPHN in the infants of mothers who used SSRI antidepressants during pregnancy.
- The risk was 1.9 in 1,000 when SSRIs were taken during early pregnancy; that is, until the 8th week of pregnancy. The risk was 3 in 1,000 when SSRIs were taken in late pregnancy; that is, after the 20th week of pregnancy. If the mother didn't take SSRIs, the risk was 1.2 in 1,000.
- The risk did not appear to differ much across different SSRI drugs; that is, sertraline was not especially associated with increased or decreased risk.
- The new study was not designed to *show* that sertraline or other SSRIs cause or do not cause PPHN. All that the study showed is that sertraline and other SSRIs were *associated with* PPHN. This means that other factors, such as the reason (eg, depression) for which antidepressants were prescribed, could also have been responsible for raising the observed risk. Driving this point home, the study found that women who had previously been admitted for psychiatric reasons had an increased risk of PPHN even if they didn't use antidepressants during pregnancy.



# Practical Psychopharmacology

4. There may be an interaction between antidepressant drugs and psychiatric illness that significantly elevates the risk (because the risk was highest in women with a previous psychiatric admission who took antidepressants during the index pregnancy). Regrettably, Kieler et al<sup>1</sup> did not provide an analysis of PPHN risk in women with a psychiatric diagnosis who did or did not have a previous psychiatric admission subcategorized by use or no use of antidepressants during pregnancy.

## Why the Findings of the New Study

### Probably Should Not Change Current Practice

1. As already listed, many explanations are possible for the increased risk of PPHN associated with SSRIs; an etiologic role for SSRIs or psychiatric illness or an interaction between the two cannot be established through observational studies such as that of Kieler et al.<sup>1</sup> It is possible that SSRI use and a history of psychiatric admission may merely be markers for unidentified behaviors or risk factors (residual confounds) that are more directly responsible for PPHN.
2. Even if SSRIs were etiologically responsible for PPHN in the Kieler et al<sup>1</sup> study, the absolute risk with late pregnancy exposure was small (0.30% against a background risk of 0.12%), and the number needed to harm (NNH) was 556. For early pregnancy exposure, the absolute risk was even smaller (0.19%), and the NNH was higher (1,429). In other words, about 500–1500 women will need to receive an SSRI during early or late pregnancy for 1 extra neonate to develop PPHN. These risks are small, given that untreated depression can have a significant adverse impact on a wide range of pregnancy outcomes.<sup>10,11</sup>

Ms M, whose case was outlined at the start of this article, asked whether she should switch to a non-SSRI antidepressant. In addition to the points discussed above, she should understand that the absence of significant risk of PPHN with “other antidepressants” in the Kieler et al<sup>1</sup> study could merely have been due to a lack of statistical power. For example, there were only 627 exposures to “other antidepressants” during late pregnancy in contrast with 11,014 exposures to SSRIs. Furthermore, relative to the literature base available for SSRIs, there is little hard information available on the safety of non-SSRI antidepressants with regard to different pregnancy-related outcomes. Finally, there is no assurance that other antidepressants will as effectively stabilize her mood disorder as sertraline appears to have done.

### Other Study-Specific Critical Comments

1. There is no assurance that women who filled a prescription for an SSRI actually took the SSRI during the period of risk. Kieler et al<sup>1</sup> observed that this is not necessarily a limitation, because if SSRIs truly predispose to PPHN, then classifying women as having received SSRIs when they did not would bias the results toward the null hypothesis. However, this argument fails if residual confounding associated with the psychiatric indication was responsible for the PPHN risk, in which case a significant result would still emerge, resulting in false implication of the SSRI. Occhiogrosso et al<sup>3</sup> provided a useful discussion on different confounds associated with depression and SSRI treatment in the context of PPHN.
2. Many analyses were probably underpowered in this study, including the analyses related to infrequently prescribed antidepressants. For example, the apparent safety of escitalopram and fluvoxamine could have been due to the low exposure to these 2 drugs.

## TALKING WITH THE PATIENT

*“Should I continue with sertraline, switch to a non-SSRI, or avoid antidepressants altogether?”*

- There’s no assurance that another antidepressant, whether SSRI or non-SSRI, would provide the same protection against depression that sertraline appears to have provided.
- Although in one analysis the risk of PPHN did stand out with sertraline, overall, the risk did not appear to differ much across the different SSRI drugs.
- The study did not find a significant risk of PPHN with non-SSRI drugs; however, it seemed that this could be because too few mothers used non-SSRI drugs during pregnancy for a risk to be reliably identified.
- The safety of non-SSRI drugs with regard to many other pregnancy outcomes is not as well known as the safety and risks associated with SSRIs.
- There are many risks to both mother and baby associated with leaving depression untreated during pregnancy.



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## Additional Comments

It has been suggested that when PPHN appears to result from SSRI exposure, there should be good chances for full recovery.<sup>2,3</sup> This suggestion is intuitively appealing. However, in the Kieler et al<sup>1</sup> study, there was a 9% mortality rate in infants who developed PPHN after exposure to SSRIs during late pregnancy; this was no different from the background rate of mortality in unexposed infants with PPHN in the same study. Kieler et al<sup>1</sup> did not present mortality data on infants who developed PPHN in other exposure groups.

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