

ORIGINAL ARTICLE

Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn

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ABSTRACT

BACKGROUND

Persistent pulmonary hypertension of the newborn (PPHN) is associated with substantial infant mortality and morbidity. A previous cohort study suggested a possible association between maternal use of the selective serotonin-reuptake inhibitor (SSRI) fluoxetine late in the third trimester of pregnancy and the risk of PPHN in the infant. We performed a case-control study to assess whether PPHN is associated with exposure to SSRIs during late pregnancy.

METHODS

Between 1998 and 2003, we enrolled 377 women whose infants had PPHN and 836 matched control women and their infants. Maternal interviews 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.

RESULTS

Fourteen infants with PPHN had been exposed to an SSRI after the completion of the 20th week of gestation, as compared with six control infants (adjusted odds ratio, 6.1; 95 percent confidence interval, 2.2 to 16.8). In contrast, 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.

CONCLUSIONS

These data support an association between the maternal use of SSRIs in late pregnancy and PPHN in the offspring; further study of this association is warranted. These findings should be taken into account in decisions as to whether to continue the use of SSRIs during pregnancy.

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PERSISTENT PULMONARY HYPERTENSION of the newborn (PPHN) occurs in an estimated 1 or 2 infants per 1000 live births and is associated with substantial morbidity and mortality.¹⁻⁴ Despite treatment, 10 to 20 percent of affected infants will not survive.^{4,5} Newborns with PPHN are typically full-term or near-term infants without associated congenital anomalies who present shortly after birth with severe respiratory failure requiring intubation and mechanical ventilation.⁶ This disruption of the normal fetal-to-neonatal circulatory transition is characterized by postnatal persistence of elevated pulmonary vascular resistance, resulting in right-to-left shunting of blood through fetal channels (the patent ductus arteriosus, foramen ovale, or both), diminished pulmonary blood flow, and profound hypoxemia.^{6,7}

On pathological study, newborn infants with PPHN are found to have congenital pulmonary vascular remodeling involving increased muscularization of the pulmonary arterioles. This increased muscularization may be due to distal extension of hypertrophied or hyperplastic arteriolar smooth muscle.⁷ Possible mechanisms leading to the maintenance of high pulmonary vascular resistance after birth may include decreased production of, or responsiveness to, vasodilators such as nitric oxide and prostacyclin; increased production of, or responsiveness to, vasoconstrictors such as endothelin and platelet-derived growth factor; or changes in the production of, or responsiveness to, both vasoconstrictors and vasodilators.⁸ However, structural pulmonary vascular remodeling clearly has a role in the pathogenesis of at least some cases of PPHN.

These findings suggest that prenatal exposures can contribute to the pathogenesis of this disorder. However, few studies have focused on risk factors for the development of PPHN. Male sex, nonvertex presentation, meconium staining of the amniotic fluid, neonatal sepsis, and pneumonia have been suggested as potential risk factors.^{6,8} Maternal risk factors include a lower educational level, fever, urinary tract infection, diabetes, cesarean section, antenatal use of nonsteroidal antiinflammatory agents (NSAIDs), and possibly tobacco use.⁶⁻¹⁰

The results of a previous small cohort study conducted by a teratogen-information service generated the hypothesis that maternal use of selective serotonin-reuptake inhibitors (SSRIs) in late

pregnancy may be a risk factor for PPHN.¹¹ Among 174 infants born to women who used fluoxetine for some portion of their pregnancies, the 73 who were exposed to fluoxetine up to the time of delivery were significantly more likely to have specific transient neonatal complications, including respiratory problems, jitteriness, and hypotonia, than the 101 infants whose prenatal exposure was restricted to the first trimester of pregnancy. Two of the 73 infants (2.7 percent) exposed to fluoxetine in late pregnancy had PPHN, as compared with none of the 101 exposed only in early pregnancy.¹¹ We conducted a study to test the hypothesis that exposure to SSRIs during late pregnancy is associated with an increased risk of PPHN. Our study is part of a large case-control study of risk factors for PPHN, conducted within the Birth Defects Study of the Slone Epidemiology Center.

METHODS

The Slone Epidemiology Center Birth Defects Study began interviewing mothers of malformed children in 1976.¹² The present analyses are based on a specially designed study, nested within the Birth Defects Study, to evaluate risk factors for PPHN, with a specific focus on exposure to NSAIDs and SSRIs during late pregnancy. Study subjects from 97 institutions in four metropolitan areas (Boston; Philadelphia; San Diego, California; and Toronto) were identified between 1998 and 2003. To identify subjects, admission and discharge records from major referral hospitals and clinics were reviewed, logbooks from neonatal intensive care units were examined, and weekly telephone calls were made to collaborators at newborn nurseries in community hospitals; the calls to community hospitals were made to identify infants with PPHN who might not have been referred to major centers. Information on healthy newborns from the same centers was also collected. Prior approval for the study was obtained from the review boards of all participating institutions. All mothers who were interviewed gave oral consent and, when it was required by institutional review boards, written consent to participation in the study.

The participation rate was 69 percent for mothers of subjects with PPHN and 68 percent for mothers of controls. After exclusion of mothers who could not be located and invited to participate, the rates were 73 percent and 71 percent, respectively.

SELECTION OF PATIENTS AND CONTROLS

The diagnostic criteria for PPHN were a gestational age of more than 34 weeks, presentation shortly after birth with severe respiratory failure, and evidence of pulmonary hypertension. Severe respiratory failure was defined as the need for intubation and mechanical ventilation. The exclusion criteria were 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. Subjects with an atrial septal defect were included because right-to-left atrial hemodynamic shunting commonly occurs among infants with PPHN, and neonatal echocardiographic studies often do not distinguish between atrial septal defects and patent foramen ovale. Infants who had isolated small muscular ventricular septal defects were not excluded, because the abnormality was thought to be a hemodynamically insignificant finding.

Pulmonary hypertension was documented either by a 5 percent or greater gradient between preductal and postductal oxygen saturation or by echocardiographic evidence. Among those who underwent echocardiography, infants were designated as having PPHN if any of the following criteria were met: the cardiologist assigned the diagnosis of PPHN or noted significant or marked pulmonary hypertension, the echocardiogram showed right-to-left hemodynamic shunting at the ductus arteriosus or at the patent foramen ovale, or the echocardiogram showed bidirectional hemodynamic shunting accompanied by leftward bowing of the ventricular septum to a degree consistent with a pulmonary arterial pressure more than half of the systemic pressure.

Records for all infants admitted to the neonatal intensive care units at participating hospitals were screened by nurses or by respiratory therapists specially trained to identify PPHN. One of the authors, a neonatologist, who was blinded to the history of maternal exposure to medications, reviewed the medical records of all patients with potential PPHN, including infants with diagnostic codes for asphyxia, cyanotic congenital heart disease, respiratory distress syndrome, pneumonia, meconium aspiration, transient tachypnea of the newborn, or pulmonary hypertension.

The control group 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). The intended ratio of patients to controls was 1:2. After the final classification of patients with confirmed PPHN and completion of the interviews, controls who were matched with these patients and whose mothers had completed the interview were selected for the analyses.

ASSESSMENT OF EXPOSURE

Within six months of delivery, trained study nurses who were unaware of the study hypothesis interviewed the mothers of the patients and the mothers of the control infants. The telephone interview was detailed and structured, and it included questions on demographic characteristics, the mother's medical and obstetrical history, the parents' habits and occupations, and the use of all medications (prescription and over-the-counter) during the period from two months before conception to the end of the pregnancy. The interviewer entered the mother's responses directly into the computer. During the interview, the interviewer had access to computerized dictionaries of drugs and diagnoses, and responses were instantaneously coded. Quality-control procedures were conducted both manually and by computer.

The mothers were asked whether they had taken any medication for depression. A list of specific antidepressant drugs was read to each mother. Any report of medication use prompted a systematic series of questions, including the brand or generic name of the drug, the indication for which it was prescribed, the form and size of the dose, the starting and stopping dates, the frequency of dosing, and the number of pills taken per day. Recall of the timing of use was enhanced by the use of a calendar that highlighted the date of the woman's last menstrual period and the delivery date.

We classified antidepressants either as SSRIs or as other antidepressants. To be consistent with our hypothesis, we defined late-pregnancy exposure as the use of an antidepressant at any time in the second half of gestation (from 20 completed weeks after the first day of the last menstrual period until the date of delivery).

STATISTICAL ANALYSIS

Multivariate conditional logistic regression was used to estimate prevalence odds ratios (which approximate relative risks for rare outcomes) and 95 percent confidence intervals for PPHN in relation

to antidepressant exposure. Risk estimates were adjusted for potential confounders. The analyses were performed with SAS for Windows (version 8.2).

RESULTS

We enrolled 637 infants with possible PPHN; the diagnosis was confirmed in 377 of the infants, 12 of whom (3.2 percent) were born after a multiple pregnancy. These 377 patients were matched with 836 controls, 17 of whom (2.0 percent) were born after a multiple pregnancy, for a case-control ratio of 1:2.2. Of the 377 patients, 60 were preterm (born after a gestation period of >34 through <37 weeks). Among infants born at term, 265 were born with a patent ductus arteriosus. The frequency of infant death up to the time of the maternal

interview was 3.0 percent in the PPHN group and 0 percent in the control group.

The specific SSRI medications that study participants reported using were citalopram, fluoxetine, paroxetine, and sertraline. Among non-SSRI antidepressants, participants reported using tricyclic antidepressants (namely, amitriptyline, imipramine, and nortriptyline), bupropion, venlafaxine, and trazodone.

Maternal factors significantly associated with PPHN in unadjusted analyses included lower educational level, black or Asian race, higher prepregnancy body-mass index (the weight in kilograms divided by the square of the height in meters), and diabetes mellitus; male infants also had increased risk (Table 1). The factors associated in unadjusted analyses with SSRI use in the control

Table 1. Selected Demographic, Maternal, and Fetal Characteristics of Study Subjects.*

Characteristic	Definite PPHN (N = 377)	Matched Controls (N = 836)	Crude Matched Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
	<i>no. (%)</i>			
Maternal education (yr)‡				
<13	133 (35.5)	228 (27.3)	1.0	1.0
13–15	106 (28.3)	234 (28.0)	0.8 (0.6–1.1)	0.8 (0.5–1.1)
>15	136 (36.3)	374 (44.7)	0.6 (0.5–0.9)	0.7 (0.5–1.0)
Maternal race or ethnic group§				
White	217 (57.6)	606 (72.5)	1.0	1.0
Black	70 (18.6)	75 (9.0)	3.0 (1.9–4.7)	2.3 (1.4–3.8)
Asian	32 (8.5)	42 (5.0)	2.3 (1.4–3.8)	2.2 (1.2–3.9)
Hispanic	45 (11.9)	91 (10.9)	1.4 (0.9–2.1)	1.1 (0.7–1.8)
Other	13 (3.4)	22 (2.6)	2.0 (1.0–4.1)	1.5 (0.7–3.3)
Maternal age¶				
≤25 yr	99 (26.3)	208 (24.9)	1.0	1.0
25–30 yr	104 (27.6)	240 (28.7)	1.0 (0.7–1.4)	1.2 (0.8–1.8)
30–35 yr	112 (29.7)	261 (31.3)	1.0 (0.7–1.4)	1.2 (0.8–1.8)
>35 yr	62 (16.4)	126 (15.1)	1.1 (0.8–1.7)	1.4 (0.9–2.3)
Maternal prepregnancy BMI				
<20	38 (10.1)	152 (18.2)	1.0	1.0
20–27	197 (52.3)	497 (59.4)	1.5 (1.0–2.4)	1.5 (1.0–2.3)
>27	134 (35.5)	174 (20.8)	3.0 (1.9–4.6)	2.6 (1.6–4.0)
Not available**	8 (2.1)	13 (1.6)	2.2 (0.8–5.9)	1.9 (0.7–5.3)
Infant's sex				
Male	239 (63.4)	410 (49.0)	1.0	1.0
Female	138 (36.6)	426 (51.0)	0.5 (0.4–0.7)	0.6 (0.5–0.8)

group included tobacco and alcohol use, maternal diabetes, a body-mass index of more than 27, and white race (data not shown). These factors have previously been associated with the use of antidepressants.^{13,14}

Table 2 presents the matched odds ratios and 95 percent confidence intervals for antidepressant use relative to no antidepressant use during pregnancy. The crude risk of PPHN associated with the use of any antidepressant at any time in pregnancy was not significantly elevated (odds ratio, 1.3; 95 percent confidence interval, 0.7 to 2.2), nor was the use of SSRIs alone at any time in pregnancy significantly associated with PPHN (odds ratio, 1.5; 95 percent confidence interval, 0.8 to 2.9). However, when the comparison was stratified according to the timing of exposure in preg-

nancy, use of any antidepressant after the 20th week of gestation was significantly associated with PPHN (odds ratio, 2.9; 95 percent confidence interval, 1.3 to 6.5). Further analysis demonstrated that this association was entirely attributable to the subgroup of infants with late exposure to SSRIs (odds ratio for SSRI use after the 20th week of gestation relative to no use in the pregnancy, 5.1; 95 percent confidence interval, 1.9 to 13.3). There was no increased risk of PPHN when SSRI use was restricted to the first half of the pregnancy (odds ratio, 0.3; 95 percent confidence interval, 0.1 to 1.1).

Adjustment in a multivariate analysis for maternal diabetes (pregestational or gestational, with or without treatment), maternal race or ethnic group, and body-mass index did not attenuate

Table 1. (Continued.)

Characteristic	Definite PPHN (N = 377)	Matched Controls (N = 836)	Crude Matched Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) [†]
	<i>no. (%)</i>			
Single or multiple pregnancy				
Single	365 (96.8)	819 (98.0)	1.0	1.0
Multiple	12 (3.2)	17 (2.0)	1.6 (0.8–3.5)	1.4 (0.6–3.2)
Maternal diabetes				
No	340 (90.2)	801 (95.8)	1.0	1.0
Yes	37 (9.8)	35 (4.2)	2.4 (1.5–3.8)	1.6 (0.9–2.8)
Maternal smoking				
Never	226 (59.9)	494 (59.1)	1.0	1.0
Before pregnancy	84 (22.3)	206 (24.6)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
During pregnancy	67 (17.8)	136 (16.3)	1.1 (0.8–1.5)	1.2 (0.8–1.7)
Maternal alcohol use				
Never	229 (60.7)	402 (48.1)	1.0	1.0
Before pregnancy	141 (37.4)	412 (49.3)	0.6 (0.5–0.8)	0.8 (0.6–1.1)
During pregnancy	7 (1.9)	22 (2.6)	0.6 (0.2–1.4)	0.6 (0.3–1.6)
Maternal NSAID use after wk 20				
No	340 (90.2)	749 (89.6)	1.0	1.0
Yes	37 (9.8)	87 (10.4)	1.0 (0.6–1.5)	0.8 (0.5–1.3)

* PPHN denotes persistent pulmonary hypertension of the newborn, CI confidence interval, BMI body-mass index, and NSAID nonsteroidal antiinflammatory drug. For each characteristic, the subgroup listed first served as the reference category for the odds ratios.

[†] The odds ratios for each characteristic have been adjusted for all others in the table. Other characteristics (e.g., family income and parity) were not significantly associated with PPHN (data not shown).

[‡] Educational level was not reported for two women in the definite-PPHN group.

[§] Maternal race or ethnic group was self-reported.

[¶] Age was not reported for one woman in the matched-controls group.

^{||} The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

** Data are missing because some women did not report their height.

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

Variable	Definite PPHN (N=377)	Matched Controls (N=836)	Crude Matched Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†	P Value‡
	no. (%)				
Maternal use of antidepressants					
Never during pregnancy	357 (94.7)	799 (95.6)	1.0	1.0	
Any time during pregnancy	20 (5.3)	37 (4.4)	1.3 (0.7–2.2)	1.4 (0.8–2.5)	0.30
SSRI	16 (4.2)	24 (2.9)	1.5 (0.8–2.9)	1.6 (0.8–3.2)	0.16
Other antidepressant	4 (1.1)	13 (1.6)	0.8 (0.3–2.4)	0.8 (0.2–2.7)	0.76
Maternal use of antidepressants					
Never during pregnancy	357 (94.7)	799 (95.6)	1.0	1.0	
Before wk 20	6 (1.6)	26 (3.1)	0.5 (0.2–1.3)	0.6 (0.2–1.5)	0.28
After wk 20	14 (3.7)	11 (1.3)	2.9 (1.3–6.5)	3.2 (1.3–7.4)	0.008
Maternal use of SSRIs					
Never during pregnancy	361 (95.8)	812 (97.1)	1.0	1.0	
Before wk 20	2 (0.5)	18 (2.2)	0.3 (0.1–1.1)	0.3 (0.1–1.2)	0.08
After wk 20§	14 (3.7)	6 (0.7)	5.1 (1.9–13.3)	6.1 (2.2–16.8)	0.001
Fluoxetine	3 (0.8)	4 (0.5)			
Sertraline	7 (1.9)	2 (0.2)			
Paroxetine	4 (1.1)	0			

* PPHN denotes persistent pulmonary hypertension of the newborn, CI confidence interval, and SSRI selective serotonin-reuptake inhibitor. For each variable, the subgroup listed first served as the reference category for the odds ratios.

† 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.

the association between exposure to SSRIs late in pregnancy and PPHN, which remained significantly elevated (adjusted odds ratio, 6.1; 95 percent confidence interval, 2.2 to 16.8) (Table 2). Inclusion of other factors in the multivariate model, such as use of NSAIDs in late pregnancy, smoking, and alcohol intake, did not substantially change the results (data not shown). The proportion of SSRI-exposed women taking another psychoactive drug in the second half of the pregnancy was similar for mothers of patients (29 percent) and mothers of controls (33 percent). Furthermore, restriction of analyses to full-term births (infants born at 37 weeks of gestation or later) resulted in a similar estimate of the odds ratio (adjusted odds ratio, 5.6; 95 percent confidence interval, 2.0 to 15.4). The association was also similar for patients with and without patent ductus arteriosus and after exclusion of mothers whose infants died (data not shown).

Although our predefined cutoff point for ex-

posure in late pregnancy was 20 weeks of gestation, 12 of the 14 mothers with late SSRI exposure whose infants had PPHN continued use of their medication at least into the eighth month of pregnancy. Post hoc analysis using a cutoff point of 26 weeks of gestation yielded identical results (adjusted odds ratio, 6.1; 95 percent confidence interval, 2.2 to 16.8). The numbers were too small to permit examination of the effects of dose size, specific SSRI used, or reduction of the length of exposure before delivery.

DISCUSSION

This large case-control epidemiologic study focusing on risk factors for PPHN showed a significant association between exposure of a mother to an SSRI during late pregnancy and the occurrence of PPHN in her infant. This finding is consistent with an earlier observation in a small cohort study.¹¹

Although our study cannot establish causality, several possible mechanisms suggest that a causal association is plausible. The lung acts as a reservoir for antidepressant drugs, and substantial accumulation of SSRIs in the lungs has been reported.^{15,16} Serotonin not only has vasoconstrictive properties that increase pulmonary vascular resistance,¹⁷ but also has mitogenic and comitogenic effects on pulmonary smooth-muscle cells.^{18,19} Thus, higher circulating levels of serotonin in the fetus and accumulation of serotonin in the fetal lung might result in the proliferation of smooth-muscle cells that is characteristic of PPHN.

Another potential pathway is through the inhibitory effect of SSRIs on the synthesis of nitric oxide, a vasodilator that appears to have a role in the regulation of vascular tone and reactivity both in utero and during postnatal life.⁷ In one study, the release of nitric oxide was inhibited in a dose-dependent fashion in synovial-cell culture medium treated with fluoxetine.²⁰ In a sample of patients with cardiac disease who were treated with paroxetine, the activity of nitric oxide synthase was inhibited and the serum levels of nitrite and nitrate were significantly decreased as compared with pretreatment levels.²¹

Our findings may be consistent with some of the transient neonatal complications noted to occur in 20 to 30 percent of newborns with late prenatal exposure to SSRIs.^{11,22-28} Mild respiratory distress, transient tachypnea of the newborn, failure to cry, and cyanosis are among the complications that are reported with increased frequency.^{11,23,24,27,28} It is possible that these respiratory problems represent the less severe end of the spectrum in a range of outcomes consistent with PPHN.

We found a nonsignificant reduction in the risk of PPHN when SSRI exposure was limited to the first half of gestation; however, this estimate was based on only two exposed patients. Our study was specifically designed to assess the association of PPHN with SSRI use in the second half of pregnancy. An alternative explanation for our results is confounding, particularly confounding by indication. However, exposure to non-SSRI antidepressants was not associated with PPHN, nor was there an association between PPHN and SSRIs when exposure was limited to the first half of gestation; these observations suggest that maternal depression was not independently associ-

ated with PPHN. Controlling for other potential confounders, including maternal body-mass index, smoking, use of NSAIDs in late pregnancy, and diabetes, did not attenuate the association between SSRI use in late pregnancy and PPHN. Although residual confounding cannot be ruled out, we believe it is unlikely that it could account for an elevated risk of this size. On the other hand, it is important to note that our findings, although statistically significant, are based on a relatively small number of exposed mothers with affected infants.

A potential limitation of this study is the retrospective design, which introduces the possibilities of inaccurate recall or recall bias. However, all interviews were conducted within six months after delivery, antidepressants are prescription medications taken over the long term, and the study interviewers specifically and similarly questioned both mothers of patients and mothers of controls regarding their use of antidepressants.²⁹ The likelihood of recall bias is reduced by the fact that neither the interviewers nor the mothers were aware of the study hypothesis at the time of the interview.³⁰ In addition, it seems implausible that there would be differential recall of the gestational timing of exposure to SSRIs and that of exposure to other antidepressants.

It is important to replicate these findings in other studies. In addition, further research should assess the relationship of different types and dosages of SSRIs with PPHN and with milder respiratory complications in newborns. Studies should also be undertaken to investigate whether there is any association between SSRIs and PPHN in the offspring of women who discontinue SSRI use late in pregnancy. Furthermore, to better identify patients who may be at risk, investigations should explore interactions between environmental and genetic factors, the latter including polymorphisms affecting the production or regulation of enzymes involved in the metabolism of SSRIs,²⁶ as well as mutations related to PPHN.

The prevalence of major depressive disorders among women of reproductive age is estimated to be between 10 and 15 percent.³¹ SSRIs are among the most common medications used to treat these disorders,^{32,33} and continued treatment may be needed throughout pregnancy for the health of the mother.³⁴ Our findings might be factored into an assessment of the benefit and risk for a par-

ticular mother. On the assumption that the relative risk of 6.1 for PPHN observed in our study is true, and that the relation is causal, the absolute risk among those who use SSRIs late in pregnancy is relatively low (about 6 to 12 per 1000 women); to put it in other terms, about 99 percent of women exposed to one of these medications late in pregnancy will deliver an infant unaffected by PPHN. Pending further studies to confirm these findings, clinicians and their patients must consider both the benefits of SSRIs in the treatment of depression and the potential risk of PPHN relative to the risks and benefits of alternative treatments or nontreatment.

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