

Selective Serotonin Reuptake Inhibitor Use in Pregnancy: Repercussions on the Oblivious Passenger

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Education Gaps

1. It is important to understand the safety profile of selective serotonin reuptake inhibitors with regard to teratogenicity.
2. It is important to understand the safety profile of selective serotonin reuptake inhibitors in the perinatal period.

Abstract

Depression is one of the most common comorbidities in pregnancy, and use of selective serotonin reuptake inhibitors (SSRIs) has become increasingly more common during this period. For this reason it is essential to understand the implications of SSRI use on fetal development and neonatal complications. As reviewed here, the preponderance of evidence suggests that the risk of teratogenicity with SSRI use is low. Poor neonatal adaptation or withdrawal syndrome is common among neonates exposed to SSRIs in the third trimester of pregnancy. However, the risk of severe neonatal adaptation syndrome, which would require neonatal intensive care, is low. The association between SSRI exposure and persistent pulmonary hypertension of the newborn remains controversial, but the evidence suggests a weak relationship with this rare outcome. The decision to initiate an SSRI in pregnancy should be individualized. Providers caring for pregnant women using SSRIs should feel comfortable discussing possible neonatal adaptation syndrome associated with the antenatal use of SSRIs, with a primary focus on appropriate treatment of maternal depression after discussion of risks and benefits.

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ABBREVIATIONS

aOR	adjusted odds ratio
CI	confidence interval
FDA	Food and Drug Administration
OR	odds ratio
PPHN	persistent pulmonary hypertension of the newborn
RR	relative risk
SSRI	selective serotonin reuptake inhibitor

Objectives After completing this article, readers should be able to:

1. Describe the influence of selective serotonin reuptake inhibitor (SSRI) use during pregnancy and its association with birth defects.

2. Describe the association between perinatal use of SSRIs and neonatal adaptation syndrome.
3. Describe the association between SSRI use in pregnancy and persistent pulmonary hypertension of the newborn.
4. Describe the effects of SSRI use on breastfeeding.

INTRODUCTION

Recent evidence suggests that approximately 10% to 15% of women will experience major depressive disorder in the perinatal period, which is at least as common as rates reported for women in nonreproductive states. (1)(2) Use of antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), also called *serotonin reuptake inhibitors*, has increased significantly among pregnant women in recent decades. (3) These agents, which traverse the placenta, have been inconsistently implicated in congenital anomalies in children whose mothers were exposed to SSRIs during the first trimester. In addition, SSRI use during and throughout pregnancy may have additional implications for neonatal outcomes. This review aims to explore the current evidence for SSRI use in pregnancy with a focus on teratogenicity, neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn (PPHN), and breastfeeding.

CONGENITAL ANOMALIES AND SSRIS

A considerable amount of literature has been published on SSRIs and birth defects with conflicting findings. The results of these studies can best be categorized under 2 headings: studies that demonstrate teratogenicity related to SSRI exposure or potential exposure (Table 1), and studies that demonstrate no evidence of teratogenicity related to SSRI exposure or potential exposure (Table 2).

STUDIES DEMONSTRATING TERATOGENIC EFFECT

Studies demonstrating teratogenicity are primarily retrospective and case control in nature, with their inherent limitations. A register-based retrospective cohort study from Denmark (N=1,051) found that for any SSRI prescription filled from 30 days before conception until the end of the first trimester, there was a higher risk for cardiovascular malformations (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1–1.8). (4) Another study in 2012 from the same database found that offspring of women filling a prescription

for an SSRI during the first trimester of pregnancy (N=4,183) had an increase in major anomalies (OR, 1.33; 95% CI, 1.16–1.53) and congenital heart defects (OR, 2.01; 95% CI, 1.60–2.53). (5) They also found an association between exposure to SSRIs in the first trimester and craniosynostosis, with an adjusted OR of 1.94 (95% CI, 1.00–3.76). A cohort study based on Danish administrative register data linked with the Danish EUROCAT that included 72,290 patients demonstrated an increased risk for severe congenital heart disease in children of women who used SSRIs in the first trimester (adjusted OR [aOR], 4.03; 95% CI, 1.75–9.26). (6)

A Nordic register-based case-control study included a sibling controlled design with 36,772 liveborn infants with presumed first-trimester exposure to any SSRI. (7) Risk estimates were increased for all major malformations combined (aOR, 1.13; 95% CI, 1.06–1.20), any cardiac defect (aOR, 1.15; 95% CI, 1.05–1.26), clubfoot (aOR, 1.34; 95% CI, 1.05–1.71), and omphalocele (aOR, 2.11; 95% CI, 1.01–4.39). However, the sibling controlled analysis that only included sibling pairs discordant for the exposure to SSRIs showed no increased risk for any of the aforementioned malformations; this suggests that the small increased risk found initially could be explained by unadjusted factors. (7)

The EUROCAT database compared SSRI exposure among cases with congenital heart defects or other malformations and controls. (8) The study failed to confirm prior associations with anencephaly, craniosynostosis, or limb reduction defects for presumed exposure to any SSRI. The study confirmed previously reported increased risk estimates for clubfoot (aOR, 2.41; 95% CI, 1.59–3.65) and renal dysplasia (aOR, 3.01; 95% CI, 1.61–5.61). The study also found heightened risk estimates for congenital heart defects combined (aOR, 1.41; 95% CI, 1.07–1.86), as well as increased risks specifically for tetralogy of Fallot (aOR, 3.16; 95% CI, 1.52–6.58) and Ebstein anomaly (aOR, 8.23; 95% CI, 2.92–23.16), neither of which had been previously reported in association with SSRIs. In addition, the risk estimates were increased for anorectal atresia and stenosis (aOR, 2.46; 95% CI, 1.06–5.68) and gastroschisis (aOR, 2.42; 95% CI, 1.10–5.29), respectively. A meta-analysis in 2013 that included 27 studies reported an association with

TABLE 1. Evidence to Support an Association Between First-Trimester SSRI Exposure in Pregnancy and Congenital Anomalies

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Wogelius et al (4)	Retrospective population-based cohort (N=151,831)	Exposure to SSRIs in any trimester	Congenital malformations	Congenital malformations associated with SSRI use in early pregnancy—aRR 1.34 (95% CI 1.00–1.79) and during the second or third month after conception—aRR 1.84 (95% CI 1.25–1.71)	Increased risk of congenital malformations after exposure to SSRIs in early pregnancy
Malm et al (9)	Retrospective population-based cohort (N=635,583)	Exposure to SSRIs during the first trimester	Congenital anomalies	Fluoxetine-associated isolated VSDs—aOR 2.03 (95% CI 1.28–3.21) Paroxetine RVOT defects—aOR 4.68 (95% CI 1.48–14.74) Citalopram NTD—aOR 2.46 (95% CI 1.20–5.07)	Fluoxetine use is associated with an increased risk of isolated VSDs Paroxetine is associated with RVOT defects Citalopram is associated with NTDs
Jimenez-Solem et al (5)	Register-based retrospective cohort (N=848,786)	Exposure to SSRIs during the first trimester vs women who paused exposure during pregnancy vs unexposed women	Major congenital malformations	CHD similar for exposed during first trimester—aOR 2.01 (95% CI 1.60–2.53) compared with paused treatment during pregnancy—aOR 1.85 (95% CI 1.07–3.20), $P=.94$	Increased risk of CHD if exposed to SSRIs throughout the first trimester, similar for women who used an SSRI but discontinued it during pregnancy
Munch et al (10)	Register-based retrospective cohort (N=1,928,666)	Maternal characteristics, maternal medical diseases, and medicine intake during pregnancy	Congenital hydrocephalus	Increased risk of isolated congenital hydrocephalus after maternal use of SSRIs—RR 2.7 (95% CI 1.5–4.6)	Significantly increased risk of isolated congenital hydrocephalus
Knudsen et al (6)	Register-based retrospective cohort (N=72,280)	Prescriptions for SSRIs filled during pregnancy	CHD	SSRI use during first trimester increased the risk of severe CHD—aOR 4.03 (95% CI 1.75–9.26)	Maternal use of SSRIs during first trimester increases the risk of severe CHD; no increased risk of septal defects was detected
Knickmeyer et al (11)	Retrospective cohort (N=189)	Prenatal SSRI exposure	Chiari I malformation on MRI scans at 1 and/or 2 years of age	Chiari I malformation—OR 10.32 (95% CI 2.04–102.46)	Marked increase of Chiari I malformation in children of depressed mothers treated with SSRIs during pregnancy
Ban et al (12)	Population-based cohort (N=349,127)	First-trimester SSRI or tricyclic antidepressants	Major congenital anomalies	Major congenital anomalies were not associated with SSRIs—aOR 1.01 (95% CI 0.88–1.17), or TCAs—aOR 1.09 (95% CI 0.87–1.38)	Major congenital anomalies risk did not increase with maternal depression or with antidepressant prescriptions

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TABLE 1. (Continued)

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Yazdy et al (13)	Population-based case control (N=2,624)	SSRI use for a greater than 30-day period in lunar months 2 and 3	Clubfoot	Clubfoot and SSRI—OR 1.8 (95% CI 1.1–2.8)	Increased risk of clubfoot occurrence in relation to SSRI use
Furu et al (7)	Population-based case control (N=2,303,647)	Use of SSRIs or venlafaxine in early pregnancy	Birth defects, with emphasis on cardiovascular birth defects	All major malformations combined—aOR 1.06 (95% CI 0.91–1.24) CHD—aOR 0.92 (95% CI 0.72–1.17) Right ventricular outflow tract obstruction—aOR 1.48 (95% CI 1.15–1.89) ASD and VSD—aOR 1.17 (95% CI 1.05–1.31)	Septal defects and RVOT defects were higher in exposed infants
Wemakor et al (8)	Population-based case control (N=2,177,9770)	First-trimester exposure to SSRIs	Specific CHD and other congenital anomalies	CHD—aOR 1.41 (95% CI 1.07–1.86) Severe CHD combined—aOR 1.56 (95% CI 1.02–2.39) Atrial septal defect—aOR 1.71 (95% CI 1.09–2.68) Tetralogy of Fallot—aOR 3.16 (95% CI 1.52–6.58) Ebstein anomaly—aOR 8.23 (95% CI 2.92–23.16) Anorectal atresia and stenosis—aOR 2.46 (95% CI 1.06–5.68) Gastroschisis—aOR 2.42 (95% CI 1.10–5.29)	Congenital anomalies associated with SSRI use include severe CHD, anorectal atresia, and gastroschisis
Bérard et al (14)	Retrospective cohort (N=18,487)	First-trimester exposure to antidepressants	Major congenital malformations	Major congenital malformations overall—aOR 1.07 (95% CI 0.93–1.22) Paroxetine CHD—aOR 1.45 (95% CI 1.12–1.88) and ASD/VSD—aOR 1.39 (95% CI 1.00–1.93) Citalopram musculoskeletal defects—aOR 1.92 (95% CI 1.40–2.62) and craniosynostosis—aOR 3.95 (95% CI 2.08–7.52)	There was no association of major congenital malformations overall and SSRI use Certain SSRI use in first trimester increases the risk of cardiac and musculoskeletal malformations, as well as craniosynostosis

aOR=adjusted odds ratio; aRR=adjusted relative risk; ASD=atrioventricular septal defect; CHD=congenital heart disease; CI=confidence interval; NTD=neural tube defect; RVOT=right ventricular outflow tract; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; VSD=ventricular septal defect.

TABLE 2. Evidence that Suggests No Association Between First-Trimester SSRI Exposure in Pregnancy and Congenital Anomalies

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Kulin et al (15)	Prospective multicenter cohort (N=267)	Exposure to fluvoxamine, paroxetine, or sertraline during the first trimester	Major congenital malformations	Congenital malformations—RR 1.06 (95% CI 0.43–2.62)	Fluvoxamine, paroxetine, or sertraline do not increase the risk of congenital malformations
Malm et al (16)	Population-based cohort (N=1,782)	SSRI purchase in any trimester	Major malformations, preterm birth, small for gestational age, low birthweight, and treatment in NICU	Major malformations purchase 4.2% vs no purchase 3.5% ($P=.6$) Treated in neonatal special or intensive care unit, third trimester purchase 15.7% vs first trimester 11.2% ($P=.009$)—aOR 1.6 (95% CI 1.1–2.2)	Use of SSRIs during pregnancy is not associated with increased risk of adverse perinatal outcome other than need for treatment in the neonatal special or intensive care unit
Wen et al (17)	Retrospective cohort (N=972)	SSRI prescription in the year before delivery	Adverse pregnancy outcomes	Major structural anomalies, exposed 2.1% vs not exposed 2.0%—aOR 0.98 (95% CI 0.59–1.64) Minor structural anomalies exposed 3.6% vs not exposed 3.4%—aOR 1.02 (95% CI 0.69–1.51)	SSRI exposure 1 year before delivery showed no increase in the risk of birth defects
Reis and Källén (18)	Retrospective cohort (N=14,821)	Reported use or prescription of antidepressants in early pregnancy	Congenital malformations	Relatively severe malformation—OR 1.08 (95% CI 0.97–1.21) Ventricular or atrial septal defect—OR 1.00 (95% CI 0.77–1.29) Paroxetine—OR 1.66 (95% CI 1.09–2.53)	No indication of a teratogenic effect Association between paroxetine use and CHD
Nordeng et al (19)	Prospective cohort (N=63,395)	First-trimester exposure to SSRIs	Congenital malformations	Congenital malformations—aOR 1.22 (95% CI 0.81–1.84) Risk of CHD—aOR 1.51 (95% CI 0.67–3.43)	Exposure to SSRIs during the first trimester was not associated with increased risk for congenital malformations or CHD
Margulis et al (20)	Retrospective cohort (N=149,464)	First-trimester SSRI use	CHD	CHD—OR 1.00 (95% CI 0.50–2.00) Septal defects—OR 1.15 (95% CI 0.46–2.87)	No association between maternal use of SSRIs in early pregnancy and CHD or septal defects in the offspring
Reis and Källén (21)	Retrospective cohort (N=10,511)	Maternal use of SSRIs, sedatives, or the combination of both	Congenital malformations and CHD	Congenital malformations—OR 1.17 (95% CI 0.70–1.93) CHD—OR 1.14 (95% CI 0.37–2.67)	No evidence of a synergistic teratogenic effect of the combination of SSRIs and benzodiazepines

Continued

TABLE 2. (Continued)

REFERENCE	STUDY DESIGN (N)	INTERVENTION	OUTCOME	RESULTS	CONCLUSIONS
Huybrechts et al (22)	Prescription-based retrospective (N=949,504)	Antidepressant use during the first trimester	Major cardiac defects	Cardiac defect—aRR 1.06 (95% CI 0.93–1.22)	No increased risk of CHD
Ban et al (12)	Population-based cohort (N=349,127)	First-trimester SSRI or tricyclic antidepressants	Major congenital anomalies	aOR 1.01 (95% CI 0.88–1.17)	Major congenital anomaly risk did not increase with antidepressant prescriptions
Norby et al (23)	Register-based prospective cohort (N=741,040)	Exposure to antidepressants in utero	Rate of admissions to NICU, infants' morbidity and neonatal interventions	Birth defects—OR 1.00 (95% CI 0.9–1.2) CHD—OR 1.00 (95% CI 0.9–1.2)	No increase in risk of birth defects or CHD
Petersen et al (24)	Prescription-based retrospective (N=209,135)	Different antidepressant exposures before and during pregnancy	Congenital heart anomalies up to 5 years of age	CHD—OR 1.00 (95% CI 0.65–1.52) Independent of antidepressant prescribing: Diabetes—OR 2.23 (95% CI 1.79–2.77) Increasing age—OR 1.01 (95% CI 1.00–1.02) Alcohol—OR 2.58 (95% CI 1.55–4.29) Illicit drug problems—OR 1.89 (95% CI 1.09–3.25) Obesity—OR 1.38 (95% CI 1.13–1.69)	No difference in congenital heart anomalies in children born to women with different antidepressant prescribing exposure status; increased risk for congenital heart anomalies in children of older women, in children of women with diabetes, body mass index >30 kg/m ² , with history of alcohol and illicit drug problems independent of the prescription of antidepressants

aOR=adjusted odds ratio; aRR=adjusted relative risk; CHD=congenital heart disease; CI=confidence interval; OR=odds ratio; RR=relative risk; SSRI=selective serotonin reuptake inhibitor.

cardiac malformations (relative risk [RR], 1.36; 95% CI, 1.08–1.71) and septal defects (RR, 1.40; 95% CI, 1.10–1.77). The authors concluded that although the RRs were statistically significant, none reached clinically significant levels. (25)

The inconsistency across these studies may potentially be explained by differences in study design, or by confounding factors, such as maternal obesity, diabetes, or coadministered medications.

STUDIES THAT DEMONSTRATE NO TERATOGENICITY WITH SSRI USE

The balance of prospective studies and meta-analyses suggest no increased risk of teratogenicity and SSRI use. In a prospective, controlled, multicenter cohort study, mothers who contacted a teratology information service regarding the use of SSRIs were followed through their pregnancies

(N=267). (15) The incidence of malformations in children born to women taking SSRIs was 4.1%, comparable to that found in the unexposed control subjects at 3.8%. The Norwegian Mother and Child Cohort Study (N=63,395) assessed infant outcomes following in utero SSRI exposure after adjusting for maternal depression, and found no increased risk of congenital malformations (5.6%) or cardiac defects (1.3%) compared with the unexposed control population at 4.6% and 0.9%, respectively. (19)

A study from Swedish national health registers that prospectively collected data on congenital malformations from 1996 to 2011 (N=70,339) found no statistically significant association between exposure to SSRIs and any relatively severe major congenital malformations (3.2%; OR, 0.94; 95% CI, 0.87–1.01), cardiac defects (1.1%; OR, 0.92; 95% CI, 0.81–1.05), or cardiac septal defects (0.78%; OR, 0.94; 95% CI, 0.80–1.14). (26)

Furthermore, a recent register-based prospective study from Sweden that included 17,736 infants exposed to SSRIs in utero found the same risk of total malformations (2.2%), cardiac defects (0.8%), and infant mortality within 28 days of birth (0.1%) compared to no SSRI exposure. (23) A nested cohort study using US Medicaid claims data (N=949,504) was consistent with the previously mentioned studies, with no increase in any cardiac malformation associated with prescription of an SSRI during the first trimester of pregnancy after adjustment for maternal illness (0.9% exposed vs 0.7% nonexposed; adjusted RR, 1.06; 95% CI, 0.93–1.22). (27)

A 2006 meta-analysis on SSRIs and pregnancy reported no difference for major malformations (OR, 1.39; 95% CI, 0.91–2.15) and cardiovascular malformations (OR, 1.19; 95% CI, 0.53–2.68). (28) A meta-analysis of 4 prospective cohort studies published in 2015 reported that there was no increased risk for presumed exposure to SSRIs and congenital cardiac defects combined, with a pooled adjusted OR of 1.06 (95% CI, 0.94–1.18). (29)

NEONATAL ADAPTATION

Poor neonatal adjustment syndrome, neonatal behavioral syndrome, or neonatal abstinence syndrome are used interchangeably to describe a constellation of signs and symptoms that occur after in utero exposure to SSRI; toxicity and withdrawal

are both potential explanations for this syndrome. (30) Multiple scoring systems have been developed to evaluate the severity of neonatal withdrawal to opiates and other substances (31)(32)(33); these scoring systems have been successfully translated to SSRI exposure. The Finnegan scoring system is one of the most widely used and comprises signs and symptoms that reflect different disturbances within the central nervous system, as well as the vasomotor, gastrointestinal, metabolic, and respiratory systems. Large cohort studies have consistently demonstrated an increased risk of developing neonatal abstinence syndrome with third-trimester use of SSRIs.

One study examined poor neonatal adaptation in 247 infants exposed to SSRIs in the third trimester who were admitted for observation after delivery. (34) Poor neonatal adaptation was defined as having a Finnegan score of at least 4 on 1 occasion during the 72-hour observation period. There were 187 infants with exposure to an SSRI; for all SSRIs combined, 127 infants had poor neonatal adaptation, but only 5 required a NICU admission. Formula feeding was associated with an increased risk of poor neonatal adaptation compared with breastfeeding or mixed feeding (OR, 3.16; 95% CI, 1.40–7.13; $P=0.003$).

Another study associated SSRI exposure during pregnancy with poorer self-regulation and higher levels of arousal in infants during the first month after birth. (35) No association was found with admission to a NICU.

TABLE 3. SSRI Use and Breastfeeding

	ANTIDEPRESSANT		SOURCE
	MALONE ET AL (36)	ACOG (37)	LACTMED (38)
Paroxetine	L2 ^a	L2	Occasional mild side effects such as insomnia, restlessness and increased crying. One of the preferred SSRIs.
Fluvoxamine	Not applicable	L2	Doses of up to 300 mg daily would not be expected to cause any adverse effects.
Escitalopram	Not applicable	L3 in older infants	Doses up to 20 mg daily would not be expected to cause any adverse effects.
Citalopram	L3	L3	Few cases of minor behavioral side effects such as drowsiness. No adverse effects on development. Not a first choice.
Sertraline	L2	L2	Rarely, preterm infants with impaired metabolic activity might accumulate the drug and demonstrate symptoms similar to neonatal abstinence. One of the preferred SSRIs.
Fluoxetine	L2 in older infants L3 if used in neonatal period	L2 in older infants L3 if used in neonatal period	Adverse effects such as colic, fussiness, and drowsiness have been reported. Not a first choice.

ACOG=American Congress of Obstetricians and Gynecologists; SSRI=selective serotonin reuptake inhibitor.

^aLactation risk categories: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated. (39)

Overall, as studies demonstrate a heightened risk for neonatal adaptation syndrome, neonates exposed prenatally to SSRIs should be evaluated for signs of adverse effects. However, the incidence and severity of these effects do not appear to be so frequent or severe that women should avoid using these medications if they are otherwise indicated. (40)

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

PPHN is a syndrome characterized by the presence of high pulmonary vascular resistance and right-to-left shunting. Contrary to the primary pulmonary arterial hypertension of the adult, the syndrome of the newborn is not defined by a specific pressure of the pulmonary circulation. Hypoxia with right-to-left shunt and absence of congenital anomalies of the heart confirms the diagnosis. An increase in PPHN associated with late (41) or early (42) exposure to SSRIs has been reported in 2 studies; other studies have not found an association. (43)(44)(45) In July 2006, the US Food and Drug Administration (FDA) issued a public health advisory about a possible link between in utero exposure to SSRIs and PPHN. (46) Subsequently, in December 2011, the FDA issued a drug safety communication that retracted this warning. (47) The FDA stated that the initial public health advisory in July 2006 about this potential risk was based on a single published study. Since then, conflicting findings have been seen in newer studies evaluating this potential risk, making it unclear whether the use of SSRIs during pregnancy can cause PPHN. The FDA concluded that given the conflicting results from different studies, it was premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. After the publication of the FDA statement, a multinational record-linkage study reported an increase in PPHN in offspring born to women who had filled a prescription for an SSRI late in pregnancy, with an aOR of 2.1 (95% CI, 1.5–3.0). (48)

Since then, a meta-analysis of 7 studies published through 2012 concluded that third-trimester exposure to SSRIs as a group was associated with PPHN (OR, 2.50; 95% CI, 1.32–4.73; $P=.005$), while first-trimester exposure was not (OR, 1.23; 95% CI, 0.58–2.60; $P=.58$). (49) Norby et al found that the rate of PPHN was increased in preterm and term infants exposed during pregnancy to SSRIs. (23) For term infants only, the rate of PPHN was higher with exposure in the third trimester compared with exposure in the first or second trimester only, with the number needed to harm of 285. It appears that there is an association between third-trimester SSRI use and PPHN, but the association is weak (OR, 2.50). Clinicians should weigh

the risks and benefits of SSRIs and this weak association with PPHN against the primary obligation to maintain maternal mood stability.

BREASTFEEDING

All SSRIs cross the blood-milk barrier and are excreted in breast milk, with an estimated relative infant dose less than 2% of weight-adjusted maternal dose. (50) SSRIs have different safety profiles with breastfeeding (Table 3). Fluoxetine and citalopram are excreted in larger amounts, reaching infant plasma levels that can exceed 10% of the maternal concentration. (51)(52) Conversely, the relative infant doses are low for fluvoxamine, paroxetine, and sertraline. (51) Adverse events in breastfed infants exposed to SSRIs through breast milk have been suspected in a few cases, more often with fluoxetine and citalopram. (52) For example, crying, irritability, decreased feeding, and diarrhea have been reported for fluoxetine, (38)(52)(53)(54)(55) while hypotonia, colic, decreased feeding, and sleep difficulties have been described for citalopram. (52)(56)(57) Some studies suggest avoidance of these drugs in the medication-naïve postpartum patient. (38)(50)(57) However, if the neonate was exposed to these antidepressants in utero, the impact of postnatal exposure through milk is much lower and breastfeeding is recommended. (38)(50)(52)

Furthermore, breastfeeding has consistently been shown to mitigate neonatal adaptation symptoms faster than formula feeding in infants exposed to SSRIs during the third trimester of pregnancy. The well-documented advantages of breastfeeding (eg, nutritional, immunologic) appear to outweigh the potential risks of SSRI use during breastfeeding. (58) Given this, both the American Academy of Pediatrics (49) and the National Institutes of Health (46) consider SSRIs compatible with breastfeeding.

CONCLUSION

The choice to initiate SSRI treatment during pregnancy must be individualized for each patient, and include a discussion with her clinician, weighing the risks, benefits, and alternatives. With regard to teratogenicity, studies vary in quality and design, but large prospective studies suggest an overall minimal increased risk to first-trimester exposure to an SSRI. From a neonatal standpoint, familiarity with potential conditions associated with antenatal exposure to SSRIs, including poor neonatal adaptation and PPHN, can guide patient counseling if medication is initiated, and improve postnatal detection and management. Given that untreated maternal depression is associated with poor

compliance to care and adverse perinatal outcomes, the balance of guidelines favor the initiation and continuation of SSRIs during pregnancy and the postpartum period when indicated.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of maternal psychiatric disorders and their treatment.

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