Antidepressant Use in Pregnancy: A Critical Review Focused on Risks and Controversies

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Abstract

Objective—Conflicting data have led to controversy regarding antidepressant use during pregnancy. The objectives of this paper are to: (1) review the risks of untreated depression and anxiety; (2) review the literature on risks of exposure to antidepressants during pregnancy; (3) discuss the strengths and weaknesses of the different study designs used to evaluate those risks; and, (4) provide clinical recommendations.

Method—MEDLINE/PubMed was searched for reports and studies on the risk of first trimester teratogenicity, post natal adaptation syndrome (PNAS), and persistent pulmonary hypertension (PPHN) with in utero antidepressant exposure.

Results—While some individual studies suggest associations between some specific major malformations, the findings are inconsistent. Therefore, the absolute risks appear small. PNAS occurs in up to 30% of neonates exposed to antidepressants. In some studies, PPHN has been weakly associated with in utero antidepressant exposure, while in other studies there has been no association.

Conclusion—Exposures of concern include that of untreated maternal illness as well as medication exposure. It is vital to have a careful discussion, tailored to each patient, which incorporates the evidence to date, and considers methodological and statistical limitations. Past medication trials, previous success with symptom remission, and women’s preference should guide treatment decisions.

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Keywords
Antidepressant; In utero; Teratogenicity; Post natal adaptation syndrome; Persistent pulmonary hypertension

INTRODUCTION
During the reproductive years a significant proportion of women experience depressive and anxiety disorders (1). Approximately 18.4% of women suffer from antenatal depression, and as many as 19.2% of mothers develop a depressive disorder within several weeks of delivery (2). Anxiety disorders are also common, with a prevalence rate of 21.7% during the 3rd trimester of pregnancy, and 11.1% during the first 3 postpartum months (3, 4).

Untreated depression and anxiety during pregnancy negatively impacts mother and fetus/child. Women are more likely to experience inadequate maternal weight gain (5) and abuse substances (6). Depression in pregnancy is also associated with preeclampsia, preterm birth (7, 8) (9) (10), increased risk for delivery of a low birth weight infant (11), elective termination of the pregnancy (12), postpartum depression (13), and anxiety. Depression is associated with fetal distress (14) and an increased risk of neonatal care unit admission and caesarian delivery (15).

Postpartum depression can negatively impact child development and has been associated with difficult infant and childhood temperament (16, 17) and attachment insecurity (16). Maternal depression may also lead to emotional and functional disability in children including cognitive delays (18), behavioral problems (16), and difficulties with social interaction (19). Children of depressed mothers are at increased risk of developmental delay, impaired language development, and lower IQ scores (20, 21). The impact of maternal depression has effects beyond infancy, as one-third of school-aged children of depressed mothers suffer from depressive, anxiety or disruptive disorders (22). Effective treatment of maternal depression mitigates this negative impact (23). Perinatal depression can also be fatal; maternal suicide accounts for up to 20% of postpartum deaths in depressed women (24).

Stress and anxiety during pregnancy influence maternal behavior and birth outcomes: maternal tobacco smoking, caffeine consumption, poor nutrition and exercise, preterm labor, preterm birth and low birth weight are associated with prenatal anxiety (25). Antenatal anxiety may increase the risk of childhood developmental and psychiatric disorders. It may adversely affect infant emotional development (26) and has been associated with reductions in gray matter density in young children (27). Treatment of perinatal depressive and anxiety disorders is of paramount importance to mitigate these risks. Despite the risk of relapse to depressive episodes and anxiety and associated adverse effects, women are likely to stop antidepressant treatment during attempts to conceive or pregnancy (28, 29).

Due to conflicting reports in the literature on the risk of first trimester teratogenicity, post natal adaptation syndrome (PNAS), and persistent pulmonary hypertension (PPHN) with in utero antidepressant exposure, a review of these topics is of great clinical importance. In this...
review, selected topics of controversy regarding antidepressant use in pregnancy are presented, in order to provide clarification during clinical decision making and risk/benefit assessment and discussion. A review of all possible outcomes is beyond the scope of this paper. Although not reviewed in this article, there are associations among antidepressant in utero exposure and measures of birth outcome, including an increased rate of spontaneous abortion (30-35) (36-39), low birth weight (35, 40, 41), and reduced gestational age or preterm birth (35, 40, 42-44) in depressed women exposed to antidepressants. Recent studies have raised questions about possible associations with antidepressant use in pregnancy, including autism (45) and effects on long-term neurocognitive development (46). While all associations with in utero exposure are important, we limited our review to topics that have become the main controversies in antidepressant use during pregnancy in recent years.

Aims

The purpose of this review is to: (1) review the risks of untreated depression and anxiety; (2) review the literature on risks of exposure to commonly used antidepressants during pregnancy; (3) discuss the strengths and weaknesses of the different study designs used to evaluate those risks; and, (4) provide clinical recommendations.

METHODS

A search was done for the English-language literature indexed on MEDLINE/PubMed for the period between 1966 and 2012 using the following key terms: antidepressant, SSRI, SNRI, noradrenergic and specific serotonin antidepressant (NaSSA), NRI, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, venlafaxine, mirtazapine, reboxetine, duloxetine, bupropion, trazodon, nefazodone, and vilazodone in association with antenatal depression, maternal, pregnancy, prenatal exposure, malformation, in utero exposure, neonatal complications, gestational, neonatal health, neonatal outcome, birth outcome, persistent pulmonary hypertension, birth defects and congenital heart defect. To determine whether other relevant articles were not identified in the initial search, all articles were cross-referenced. Original observational studies, case reports and case series were included.

RESULTS

First Trimester Exposure: Is There Evidence of Teratogenicity?

In the U.S., approximately 1 in every 33 infants (3%) is born with a major birth defect (47). Major birth defects or malformations typically require medical or surgical intervention for a structural or functional abnormality. Antidepressants that affect serotonergic tone could putatively increase the incidence of congenital malformations because serotonin is important in aspects of early embryonic development that impact development of the neural tube, branchial arch and heart.

Despite the high prevalence of birth defects overall in the population, each specific type of major birth defect is generally rare, and studies that are inadequately powered or controlled may overestimate risk and association. For example, of the major birth defects studied in association with antidepressant use, omphalocele occurs in 1 per 5,386 births, gastroschisis

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occurs in 1 per 2,229, anencephaly 1 in every 4,859, and craniosynostosis in 4-10 per 10,000 births in the general population (47). While congenital heart disease is relatively common (48, 49), studies examining the effects of drug exposure should ideally use the rate of unexposed infants with identical ascertainment methods as a comparison rate for the malformation(s) under study, rather than the 1% incidence of congenital heart disease (48, 49) in the general population which makes interpretation of findings difficult.

Different methodologies have been used to study the risks of teratogenicity with antidepressant use in pregnancy. Some use retrospective case-control studies, which carry the risk of recall bias and large non-response rates. Other prospective controlled studies, often performed in teratology information centers, use detailed drug use information in a small number of women. A final type of study uses data from drug registries and administrative data bases, which carry the risk of exposure misclassification given that it is not clear whether women who purchased the drug took it as prescribed. When they recently compared interview data with data from a prescription registry, Kallen et al. found the most valid results are obtained through prospective interview data on drug use. For prescription data, they recommended avoiding the use of prescriptions given earlier than 1 month before the last menstrual period due to the increased percentage of women who did not use the medication in pregnancy (50).

Across all study types, the risks of the underlying untreated disorder and other associated confounding factors are rarely taken into account. The strategy of using depressed women without drug treatment as a comparison may not be adequate given the likelihood that illness severity co-varies with medication use. Comparisons of different SSRI effects may also be complicated by the fact that this class of medications is used for many conditions other than depression, including anxiety disorders (51). SSRI preference may also differ according to indication, and prescribing patterns may differ between populations. In order to control for maternal illness severity, Oberlander et al. used a propensity score method that allowed them to control for maternal illness severity and other characteristics that impact neonatal outcomes. Unfortunately, even with their large population level data set, propensity score matching led to a reduced sample size for comparison groups (52).

The use of different study designs and limitations of each may explain why findings of malformations are inconsistent. At present, data are difficult to interpret because it difficult to differentiate whether adverse outcome are associated with underlying illness, the medication itself or other unknown factors associated with either or both.

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

Prior to 2005, studies had not suggested an increased risk of major congenital malformations with in utero exposure to SSRIs (35, 36, 43, 53-59). These studies, as well as those since, were generally limited by insufficient power, confounding variables, concerns with the method of birth outcome classification and limited exposure information (60). Over the past several years, a number of studies have found associations between specific SSRIs and malformations, although the findings are inconsistent across studies, making their interpretation difficult. A teratogen would be expected to cause a similar type of
malformation consistently across studies. While this has not been the case with SSRIs, sporadic reports have generated concerns.

Since 2005, the data have been conflicting and inconsistent (61) with regard to whether individual SSRIs are associated with an increased risk of congenital malformations. Discrepant findings have fueled confusion, and it is unclear whether un-replicated results represent true associations. One example of conflicting findings are the retrospective case-control studies by Alwan et al. and Louik et al. which linked the use of SSRI drugs to rare malformations. Both studies carry a risk for recall bias and have a high rate of non-responders (60, 62). Other studies have other methodological limitations, for example, Wogelius et al. (63) identified malformations from discharge diagnoses in women with and without intrauterine SSRI exposure. Examining physicians were aware of SSRI exposure which may have increased vigilance during exams, and led to surveillance bias and overestimation of risks due to the identification of less serious malformations, e.g., mild cardiac defects that would not otherwise have been identified. Other studies are so small that they lack statistical power to detect anything but extreme risk increases that are unlikely to occur with SSRI exposure.

A small increased absolute risk of rare defects such as omphalocele, anencephaly, craniosynostosis, (60), cystic kidney and congenital heart defects (51, 64-66) has also been reported. Importantly, specific patterns of congenital malformations have not been demonstrated with SSRIs across studies, and teratogenicity is usually determined by a consistent risk and pattern of malformation. Among the SSRIs, paroxetine has become the most complicated in terms of reported risks and recommendations for use in pregnancy.

Paroxetine—In 2005, a small study performed by GlaxoSmithKline suggested an increase in cardiac malformations in infants exposed to paroxetine in utero compared with controls. As a result, GlaxoSmithKline modified the prescribing information to include a warning regarding the risk of cardiac malformations with antenatal paroxetine exposure. This study was not peer-reviewed or published, but was presented to the U.S. FDA and cited elsewhere (67). As this recommendation was based on non-peer-reviewed, unpublished data, and a relatively small sample size, its findings are difficult to interpret (68). Since then, multiple studies (41, 51, 60, 66, 69-73), although not all (65, 74), have found an association between prenatal paroxetine exposure and an increased risk of congenital malformations, yet the causality and magnitude of that risk are unclear.

A recent meta-analysis based on research prior to 2006, found that paroxetine was associated with 1.7 fold risk increase of cardiac malformation (71). A later review, however, concluded that is not practical to use a meta-analysis to examine the safety of paroxetine in pregnancy given the limitations in the methodology of the published studies (75). Another meta-analysis that examined 37 studies from January of 1992 through September 2008, provides further evidence of an increased risk of major congenital malformations with paroxetine exposure. The authors concluded that first-trimester paroxetine exposure is associated with an increased prevalence of combined cardiac defects (prevalence odds ratio (POR) = 1.46%; 95% CI 1.17-1.82) and aggregated defects (POR=1.24; 95% CI 1.08-1.43) (70).
Other SSRIs—Specific individual studies have found malformations associated with specific SSRIs as isolated reports. These include hypertrophic stenosis (76), congenital heart defects, and other major abnormalities (41, 65, 73, 77) with fluoxetine, omphalocele (62, 77-79) and cardiac septal defects (62, 77, 79) with sertraline, and omphalocele (62, 77-79), congenital heart defects (62, 77, 79), and neural tube defects (73) with citalopram. Other studies however, have not suggested an association between fluoxetine (62, 64, 69, 77-84), sertraline (41, 51, 69, 73, 80-84), or citalopram (41, 80-82, 84) and major congenital abnormalities. While the data are very limited, escitalopram has not been associated with risk of major malformation (62, 73, 81, 85).

Meta-analyses—When interpreting this data, it is imperative to consider meta-analyses, because the power of individual studies may not be adequate and large numbers of subjects are needed to demonstrate association with congenital malformations. Five meta-analyses have investigated the risk for major malformations in association with antidepressant use during pregnancy. Four of these studies found no statistically significant increased risk of major malformations in the first trimester of pregnancy (31, 86-88). The fifth meta-analysis found an increased risk of cardiac malformations in infants exposed to paroxetine in the first trimester (71).

In summary, paroxetine and other SSRIs have not consistently been demonstrated to be associated with particular birth defects. Paroxetine use during early pregnancy has been the most controversial, as it has been associated with an increased risk of overall major malformations, particularly atrial and ventricular septal defects in several studies (51, 60, 66, 69, 72), but assessments of large databases have not supported this finding (65, 74).

Serotonin-norepinephrine reuptake inhibitors (SNRIs), Norepinephrine reuptake inhibitors (NRI) and other antidepressants

Compared to the SSRIs, there are fewer reports on the reproductive safety profiles of other antidepressants. While the available evidence is extremely limited, studies examining venlafaxine, duloxetine, nefazodone, and mirtazapine do not suggest an increased risk of congenital malformations (39)(81)(89)(90). An increased risk of left outflow tract heart defects has been inconsistently demonstrated in association with bupropion. Overall, the limited studies have shown reassuring, but not definitive data regarding the reproductive safety of venlafaxine, trazodone, mirtazapine, and bupropion.

Bupropion—Bupropion has efficacy for smoking cessation, and tobacco use is associated with birth complications. Understanding the safety of bupropion in pregnancy is important as it may be a potential treatment option for women with depression and nicotine dependence. In 1997, GlaxoSmithKline established a Bupropion Pregnancy Registry and by March 2008, 3.6% and 1.3% of infants exposed to bupropion were reported to have congenital abnormalities and congenital heart defects, respectively. Congenital heart defects were found in both retrospective and prospective reports (91), raising concern that first trimester bupropion exposure might increase the risk of congenital heart defects. The first prospective study on bupropion use in pregnancy did not demonstrate an increased risk of major malformation with bupropion exposure, however, the sample was small with only
enough power to detect a 5-fold increased risk (37). A retrospective case-control study that examined the risk of bupropion exposure 1 month prior to conception until 3 months after conception found that exposed infants were more likely to have left outflow tract heart defects, but not other defects (OR=2.6; 95% CI 1.2-5.7) (92). Another case-control study did not find an increased risk of congenital malformations when they compared first trimester bupropion exposure to: (1) first trimester exposure to other antidepressants; and, (2) bupropion exposure outside the first trimester (93). Other studies (37) (92) are reassuring as they do not demonstrate an increased risk of congenital malformations following exposure to bupropion during pregnancy. Even with the the possible increased of congenital heart defects (91, 92), the absolute risk of a congenital heart defect remains low at 2.1/1000 births in exposed infants (92) when compared to the estimated prevalence of 0.82/1000 births in the general population (49).

**SNRIs and other non-SSRI antidepressants**—There are a very limited number of studies examining SNRIs (such as venlafaxine and duloxetine). A large prospective cohort study that included the SNRI venlafaxine, and other non-SSRI antidepressants -mirtazapine, nefazadone, bupropion and trazodone - found that the prevalence of cardiac malformations was well below the prevalence rate at 0.6% in the antidepressants as a group (81). Data obtained from the Swedish Medical Birth Registry also do not suggest an increased risk of congenital malformations after exposure to SNRI/NRIs. However, due to small sample size it only would have detected a marked teratogenic effect (89).

**Mirtazapine**—A prospective, comparative study that examined whether exposure to mirtazapine during organogenesis increased the rate of major malformations, found that mirtazapine was not associated with an increased risk of major malformation (39).

**Trazodone/Nefazodone/Vilazodone**—Data on trazodone and nefazodone are limited with the exception of a multi-centre prospective controlled study which found that trazodone and nefazodone did not increase the rates of major malformation above the baseline (90). A literature review did not reveal any data on vilazodone.

**Summary**

Recently, the safety of SSRIs in pregnancy has been challenged by data from large population-based studies. Reports are difficult to interpret due to the lack of consistent findings and the inability to assess cause and effect from association studies. Most reports do not take into account the underlying psychiatric condition and variables that may not be controlled for that would differ between groups being compared. While some individual studies suggest associations between SSRIs and some specific major malformations, the findings are inconsistently observed, therefore the absolute risks appear small. While the limited available data suggest a possible association between bupropion and congenital heart defects (91, 92), the absolute risk appears low. Although the very limited studies examining SNRIs have been reassuring, further investigation is needed before the risks associated with their use may be fully understood.
Later Pregnancy Controversies

Post Natal Adaptation Syndrome (PNAS)—All SSRIs cross the placenta, carrying the potential to increase serotonin concentrations in the developing fetus. Increased serotonin concentrations may impact fetal cardiovascular, respiratory and neurological development, which all involve serotonin. Premature neonates may be more susceptible to PNAS given their immature lung and central nervous systems.

Since PNAS was first noted in 1973 (94), exposure to antidepressants during late pregnancy has been associated with infant irritability, abnormal crying, tremor, lethargy, hypoactivity, decreased feeding, tachypnea, and respiratory distress (95-99). As data emerges, this cluster of symptoms is increasingly referred to as PNAS. It has also been referred to as “neonatal behavioral syndrome” or “poor neonatal adaptation syndrome” with studies focusing on a collection of symptoms including irritability, tachypnea, hypothermia, and hypoglycemia (96, 100-102). Clinical signs and symptoms usually develop from birth to days after delivery and are time-limited. While they usually resolve within days or weeks of delivery (95), symptoms have been reported to last as long as 6 weeks (103). Severity and length are impacted by multiple factors including dose, timing and duration of exposure and SSRI pharmacology including half-life, presence of active metabolites, and maternal and infant hepatic cytochrome P450 isoenzyme genotype, among others (104).

Different methodologies have been used to examine the relationship between PNAS and antidepressants. Databases of adverse drug event reports have the advantage of being able to detect effects too rare to be detected in clinical trials. Similar to case reports, however, databases of adverse drug reaction reports are limited by lack of incidence rate determination, underreporting and reporter bias (95). The identification of PNAS symptoms related to antidepressant exposure is also complicated by the challenge of determining whether the symptoms are due to maternal illness or medication exposure (105). Important considerations in evaluating the data include: 1) whether systematic assessments of infant were conducted, 2) whether appropriate control groups were included in the study, 3) whether raters of the infants were blinded to antidepressant exposure, 4) whether maternal diagnosis or symptoms were taken into consideration, and 5) whether other confounding variables may contribute to neonatal symptoms.

Numerous mechanisms have been proposed for PNAS including serotonin toxicity (104), overstimulation of serotonin (101), and infant genotype (106). Many PNAS symptoms overlap those found in adult SSRI discontinuation syndrome, cholinergic overdrive and serotonin syndrome. Several case reports note infant toxicity after in utero exposure to paroxetine (106), and fluoxetine (97, 107-109). Several of those reports note elevated infant serum levels, supporting toxicity as the cause (97, 107, 108, 110). Other reports document discontinuation symptoms following in utero antidepressant exposure (110), specifically with sertraline (111), paroxetine (98-100, 112, 113), and venlafaxine (114).

In 1996, Chambers et al published the first cohort study examining PNAS and found that late pregnancy exposure to fluoxetine was associated with an increased special care nursery admission rate when compared to exposure earlier in pregnancy (35). A similar study that retrospectively compared exposure to fluoxetine early and late in pregnancy found an.
increased risk of special care nursery admissions after late pregnancy exposure to fluoxetine (115).

Another study that prospectively compared neonatal complications in infants found that third trimester paroxetine exposure had a high rate of neonatal complications compared to controls (22% vs. 5.5% respectively) (102). Using the same definition as Chambers et al, Oberlander et al found that thirty percent of infants exposed to SSRI alone or in combination with clonazepam showed symptoms of poor neonatal adaptation, 25% and 39% respectively (104). Another hospital based cohort study found PNAS in 30% of infants exposed to SSRIs (116). This rate of 30% is higher than found by Costei et al (22%) (102), and Hendrick et al (10.5%) (55) but very similar to that found by Chambers et al (31.5%) (35) and Oberlander et al (30%) (104). The data collected by Costei may not represent the true rate as data were collected later after delivery and cases may have been missed. A retrospective chart review study reported a higher rate of behavioral signs (77.6%) in SSRI exposed infants compared to 41% of the nonexposed (117).

In a prospective comparison study, using cord blood levels of 5-Hydroxyindoleacetic acid (5-H1AA) and a modified Serotonin Syndrome Scale, infants exposed to citalopram or fluoxetine in late pregnancy had lower Apgar scores and more serotonergic symptoms than infants not exposed (101). Other prospective studies have also found that third trimester exposure to antidepressants is associated with PNAS symptoms (118) and greater special care nursery admission rates (119). While it lacked statistical significance, a prospective controlled cohort noted a trend for increased risk of PNAS symptoms in infants exposed to antidepressants in the second and third trimester. Mild symptoms may have been underreported due to recall bias during data collection interviews with mothers (120).

SSRIs and SNRIs may both cause PNAS symptoms. A prospective observational study comparing placental transfer and neonatal effects of SSRI and SNRI (venlafaxine) exposure in pregnancy to non-exposed matched controls found that both SSRIs and venlafaxine transferred across the placenta and were associated with PNAS symptoms (121). An analysis of the World Health Organization adverse events database reported 94 cases of PNAS after in utero exposure to SSRIs and venlafaxine. PNAS symptoms in infants were noted after maternal fluoxetine, citalopram or paroxetine exposure (100). However, the total number of women using these medications was not reported, so the incidence of neonatal symptoms was not possible to ascertain.

In 2004, the FDA suggested (122) providers consider tapering antidepressants in the third trimester. While discontinuation is intuitive if antidepressants are associated with neonatal symptoms, this recommendation did not receive formal clinical study prior to its release. Since this recommendation, Warburton (2010) and colleagues assessed babies of mothers who were not exposed to antidepressants in the last 14 days of pregnancy compared to those who were not exposed and factored in maternal psychiatric symptoms and other possible confounding variables into their analysis. After accounting for confounding variables, there was no difference in PNAS among women exposed to antidepressant in the last 14 days of pregnancy when compared to those who were not. However, the total number of women using these medications was not reported, so the incidence of neonatal symptoms was not
possible to ascertain (52). This study was also limited by the inclusion of subjects on fluoxetine, which may have been in the subjects’ system given its long half-life of two weeks.

PNAS appears to be multifactorial in nature, with late pregnancy antidepressant use accounting, in part, for neonatal symptoms. It is important to consider that maternal anxiety has also been associated with changes in infant behavior and self-regulation (123). Exposure to antidepressants in pregnancy, regardless of timing, has been associated with PNAS. While the available evidence is conflicting, the overall data suggests that PNAS can occur in neonates exposed to SSRIs and SNRIs, yet have most often been reported after exposure to paroxetine, fluoxetine and venlafaxine (84, 120).

**Persistent pulmonary hypertension of the newborn (PPHN)—**Pulmonary hypertension is a normal and required state for the fetus in utero because the placenta, as opposed to the lung, is responsible for gas exchange. At birth, the lung replaces the placenta as the primary site of gas exchange, and there is a rapid drop in pulmonary vascular resistance and a resultant increase in pulmonary blood flow. Multiple chemical pathways are responsible for this cardiopulmonary transition (124).

PPHN can result whenever cardiopulmonary transition does not occur. PPHN is a rare disorder that occurs in approximately 1-2 per 1000 births (125). Reduced length of gestation and premature birth has been associated with increased risk of PPHN (121). Infants with PPHN present within twelve hours of birth with cyanosis and mild respiratory distress and can develop severe respiratory failure requiring intubation and mechanical ventilation (126). Even with therapy, PPHN can be fatal in approximately 10-20% of cases (127), depending upon the etiology (128). Approximately 25% of infants with moderate to severe PPHN will demonstrate significant neurodevelopmental impairment at 12-24 months (129).

Respiratory insufficiency is one symptom of PNAS and may represent the presence of a mild form of PPHN and not PNAS, per se (130, 131). It is not certain that SSRIs are associated with the development of PPHN, but there is some evidence that longer periods of in utero SSRI exposure may be associated with increasing risk, and severity, of neonatal respiratory complications (132). How SSRIs may affect neonatal respiratory complications is under investigation. The accumulation of SSRIs in the lungs may result in high circulating levels of serotonin which, through its vasoconstrictive effects, increases pulmonary vascular resistance and may cause proliferation of smooth-muscle cells in the fetal lung (133), but not all studies have found elevated serotonin levels (134). Another possible mechanism may involve the inhibitory effect of SSRIs on nitric oxide synthesis, an essential vasodilator which regulates vascular tone (135) but other studies do not support that hypothesis (134). Importantly, through unidentified mechanisms, depression and the use of SSRIs during pregnancy have been associated with a reduced length of gestation and increased risk of premature birth (84) which itself is associated with an increased risk of PPHN. Additionally, genetic factors contribute to the risk of developing PPHN (128). Functional polymorphisms in the serotonin transporter promoter region may modulate the risk of PPHN in both adults (136) and infants with in utero exposure to SSRIs (128, 137).
In 1996, Chambers and colleagues first reported that late in utero exposure to fluoxetine was associated with an increased risk of PPHN when compared to first trimester exposure (2.7% vs. 0%), especially when compared to the prevalence found in the general population (0.07% - 0.10%) (35). A subsequent case-control study found that SSRI use after the 20th week of pregnancy was significantly associated with PPHN (adjusted odds ratio (AOR) = 6.1), but use of SSRIs or other antidepressants prior to 20 weeks gestation was not (138). A retrospective analysis of data from the Swedish Medical Birth Register also found an association between PPHN and maternal SSRI use during early pregnancy (relative risk (RR)=2.4) and late pregnancy (RR=3.6), though the absolute risk was small (139). This group’s most recent analysis which also included tricyclics, monoamine oxidase inhibitors, SNRIs and other antidepressants demonstrated an increased relative risk of PPHN for antidepressant exposure in early pregnancy (RR=2.30), for later exposure (RR=2.56) and for both early and later exposure (RR=3.44) (41).

Most of the above studies (41, 140, 141) restricted their analyses to infants delivered after 34 completed weeks gestation since shorter gestation is associated with an increased risk of PPHN. A recent population-based cohort study used national health register data demonstrated an increased risk of PPHN associated with SSRI prescription after 20 weeks gestation and before 8 weeks gestation (142). The risk of PPHN associated with exposure to individual SSRIs were of a similar magnitude, suggesting a class effect. This study restricted their analyses to infants delivered after 33 weeks gestation and was the largest completed study of the relationship between in utero SSRI exposure and PPHN.

Other studies have suggested no association between antidepressant use during pregnancy and PPHN. Two studies (143) (144) compared the prevalence of PPHN among infants whose mothers were exposed to antidepressants in the third trimester of pregnancy compared to infants not exposed and did not find any difference. The Wichman et al. study (144) is limited by a lack of delineation between women treated in late pregnancy and during the first trimester. Because late trimester use has been identified as a possible risk factor for PPHN, the inclusion of women who were treated in the first trimester may have contributed to the negative finding. Additionally, the small size of both of these studies makes it likely that a possible association would have been missed. Most recently a case-controlled study of 11,923 births, including 20 cases of PPHN, demonstrated an increased risk of PPHN with cesarean delivery prior to the onset of labor (OR=4.9) but not with SSRI use during the second half of pregnancy (145).

In 2006, based on data from the Chambers et al study, the FDA published a Public Health Advisory regarding an increased risk of PPHN associated with the use of SSRIs after the 20th week of pregnancy. This advisory resulted in changes to drug labeling to include a risk of PPHN with the use of antidepressants during late pregnancy. In December 2011, the FDA released a Drug Safety Communication (146) which stated that there is insufficient evidence that antidepressant exposure during pregnancy causes PPHN. This recent statement is an accurate reflection of the current literature which has reported either a small association between PPHN and maternal antidepressant use during pregnancy or no association.
Although studies have also reported an association between mode of delivery and PPHN (140, 141, 147-149), several were small and lacked control groups. Studies which have investigated the role of cesarean delivery and the risk of PPHN are limited because it is not clear whether the risk of PPHN is increased secondary to the mode of delivery or intrauterine fetal distress.

**CLINICAL IMPLICATIONS AND DISCUSSION**

The treatment of women during pregnancy is complex and clinical decisions should be based on the risks, benefits and alternatives to psychopharmacological treatment. All risks need to be considered, including those of untreated maternal psychiatric illness and the known and unknown potential risks of psychotropic medication. In order to provide optimal clinical care to women and their developing child, it is imperative to consider risks of treatment in the context of illness severity, consequences of no treatment and under-treatment and individual treatment preferences.

**Interpreting a Conflicting Evidence Base**

Clinicians face the challenge of interpreting an expanding and sometimes controversial evidence base. Comparing the available studies is difficult due to methodological weaknesses and differences in study design, outcome measures and exposure (72). This underlines the inherent and varying difficulties conducting epidemiological studies of this nature. In such a complicated area of study, no individual study is definitive. Statistical significance does not necessarily translate into a valuable clinical or epidemiological finding. For example, an OR of 1.2 compared to 1.7 may be statistically significant, yet not important from an epidemiological or clinical perspective.

The current evidence for malformations is limited because of inconsistent findings and limited methodology of the published studies (150). Few studies have controlled for maternal illness and therefore do not take into account whether reproductive outcomes are due to maternal illness or antidepressant exposure. Many studies also group malformation types together in order to detect a difference in risk. For example, some studies have grouped together all septal defects or congenital heart disease, encompassing a variety of birth defects and a range of severity. As a result, it is not known whether or not the reported increased risk for cardiac defects is for minor, moderate or severe forms, which each carry varying medical risks to the infant. Larger sample sizes are required to improve identification of particular teratogenic patterns, so that specific birth defects associated with antidepressants can be isolated consistently and reproduced across studies. While the large studies that do not show evidence of teratogenicity are reassuring, the literature also contains a number of studies that suggest concerns.

The current evidence base for PNAS also has limitations in that it does not: (1) systematically assess infants; (2) use appropriate control groups; (3) use blind raters of the neonates; and, (4) take into account maternal diagnosis or symptoms or other confounding variables. Despite these limitations, these study findings vary less than that of the teratogenicity or PPHN studies, and therefore more strongly suggest an association between antidepressant use in pregnancy and neonatal behavioral symptoms.

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Similarly, the PPHN literature is limited by small and/or uncontrolled studies. There are other reported risk factors, including race, method of delivery, obesity, asthma, and diabetes (141) that many studies do not take into account. While the PPHN literature is inconclusive, the available evidence reports either a small association between PPHN and maternal antidepressant use during pregnancy or no association.

**Clinical Importance of Results**

Given the inconclusive evidence, it is vital to have a careful discussion tailored to each patient that incorporates the evidence to date on the risks and benefits of antidepressant use in pregnancy. We recommend educating women about the risks of exposure to antidepressants throughout pregnancy, which should include the U.S. Food and Drug Administration categorization. Unfortunately, the U.S. FDA antidepressant risk categorization is limited, and does not adequately inform the decision making process. The limitations of this system include lack of a requirement for systematic human data, lack of clear differentiation between pregnancy categories, lack of incorporation of risks of the maternal illness and potential benefits of the medication. Newer drugs are usually much more poorly studied in human pregnancy, as little human data are required before a drug comes to market. Therefore, health care providers and patients who rely on the U.S. FDA categories may receive an oversimplified and often inaccurate assessment of the knowledge base regarding a specific medication in human pregnancy. Despite numerous studies, information regarding possible teratogenicity of antidepressants has not been updated since an FDA public health advisory in 2005 was released concerning paroxetine and the possible associated risk of increased cardiac malformations. The FDA is currently working on risk categorization that will include more meaningful and useful information to clinicians (151). However, with the current limitations of the FDA categories, it is crucial to incorporate the current research literature into the decision making and informed consent process.

**Translating Results into Clinical Practice**

We recommend weighing the risks and benefits of treatment with antidepressants during pregnancy while carefully considering the risk of untreated illness. What poses a greater risk: exposure to untreated illness or the antidepressant? If the benefits of treatment outweigh the risks, then the medication should be prescribed based on an individualized risk/benefit assessment and discussion. Past medication trials and previous success with symptom remission and women’s preference should guide treatment decisions. In order to avoid exposure to more than one antidepressant or undertreated illness one should choose a medication with known efficacy for individual women. The goal of treatment should be to maximize non-medication evidence based treatments, such as specific forms of psychotherapy, and remission of the maternal symptoms, with judicious use of pharmacotherapy when indicated.

Unless there is a reason to use another class of antidepressant, SSRIs are generally considered first-line in pregnancy. SSRIs, are well characterized, and even though risks have been reported, the preponderance of data is reassuring. It makes less sense to preferentially use a medication with less available human data. When selecting an antidepressant for a pregnant woman who has not had past medication trials, many providers prefer fluoxetine.
because of the amount of data available and lack of long term developmental sequela in children (152). A current response or history of a positive response to medication should help determine which medication to continue or initiate. The benefits of discontinuing an effective medication often do not outweigh the risks of relapse or of exposing mother and fetus to a second antidepressant medication during pregnancy.

In order to maximize treatment of depression and minimize risks of maternal and fetal exposure to antidepressants and untreated depression, women should receive the minimal effective dose of an antidepressant. The increased dose requirements across gestation (153) (154) should be considered and weighed against the risks when determining the minimal effective dose. It is also important to avoid under-treatment as residual depression and medication exposure represent dual exposures for the fetus.

Polypharmacy with multiple psychotropic medications should also be avoided, unless there is a clear indication for the use of multiple pharmacotherapies. Some studies suggest that the use of SSRIs in combination with benzodiazepines may increase the risk of congenital heart malformations (77) and PNAS (104). Another study did not demonstrate an increased risk of congenital malformations after exposure to multiple antidepressants (82). It is important to consider that approximately 50% of pregnancies are unplanned and many women enter the first trimester on several medications. For example, a positive response to taking two antidepressants concurrently may indicate that the risk of relapse with discontinuation of either outweighs the risk of polypharmacy.

Despite the FDA’s suggestion in 2004 (122) that providers consider tapering antidepressants in the third trimester, there no evidence suggesting this approach reduces the incidence of PNAS or improves infant outcomes. It also carries the risk of precipitating relapse or postpartum depression, particularly in high-risk individuals (52, 95).

Individualized treatment recommendations or plans should aim to diminish both the risk of exposure to untreated illness and the antidepressant. Exposure to untreated illness can be mitigated by preconception counseling, psychoeducation regarding risks and benefits of treatment and no treatment, close clinical monitoring, and a careful treatment plan tailored to the each woman (155). The risks associated with antidepressant use can be mitigated by using antidepressants with reassuring human data, using the minimal effective dose and avoidance of polypharmacy. Outcomes for mother and child can be optimized by the utilization of multidisciplinary approach that takes into account risks of treatment and no treatment and each woman’s preferences for treatment. This can be accomplished by a careful discussion, tailored to each patient, which incorporates the evidence to date and considers methodological and statistical limitations. Past medication trials, previous success with symptom remission, and women’s preference should guide treatment decisions.

REFERENCES


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128. OCCHIOGROSSO M, OMARAN SS, ALTEMUS M. Persistent Pulmonary Hypertension of the Newborn and Selective Serotonin Reuptake Inhibitors: Lessons From Clinical and Translational Studies. AJ Psychiatry. 2011


No single type of malformation has been consistently observed across studies with any commonly used antidepressant. Some individual studies suggest associations between particular SSRIs and specific birth defects.

SSRIs remain the most studied antidepressants in pregnancy. Less data are available for SNRIs, mirtazapine, nefazodone, trazodone and vilazodone.

Post natal adaptation syndrome (PNAS), occurs in up to 30% of neonates exposed to antidepressants in late pregnancy.

The current evidence base is limited by data that do not: (1) systematically assess infants; (2) use appropriate control groups; (3) use blind raters of the neonates; (4) take into account maternal diagnosis or symptoms or other confounding variables.

Some studies find a small association between PPHN and SSRI use, although other studies do not.

The evidence regarding the risk of PPHN due to in utero antidepressant exposure is inconclusive.
## Table I
Maternal use of antidepressants and the risk of congenital defects

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant Studied</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Pedersen LH, et al., 2009    | Population-based, cohort study | fluoxetine, citalopram, paroxetine, sertraline | 493,113 unexposed infants and 1,370 infants exposed to SSRI | • increased prevalence of septal defects with prescription of < 1 SSRI (2.1%) vs. a single SSRI (0.9%) vs. not prescribed an SSRI (0.5%)  
• increased prevalence of septal heart defects after first-trimester exposure to sertraline (1.5%) or citalopram (1.1%) yet not fluoxetine (0.6%) or paroxetine (0.3%)  
  overall no association with major malformations or non-cardiac malformations |
| Wogelius P, et al., 2006b    | Population-based, cohort | fluoxetine, citalopram, paroxetine, sertraline | 150,780 women with no SSRI prescription vs. 1,051 women who filled SSRI prescription 30 days before conception to end of first trimester vs. 453 filled prescription during second or third trimester | • increased risk of congenital malformations with prescribed SSRI early in pregnancy compared to unexposed infants (3.4% vs. 4.9%), (aRR=1.34; 95% CI 1.00-1.79) and late in pregnancy (6.8%) (aRR=1.85; 95% CI 1.25-2.71)  
• SSRI use not associated with any specific malformation |
| Wen SW, et al., 2006         | Population-based, cohort | fluoxetine citalopram paroxetine sertraline fluvoxamine | 972 women exposed to an SSRI; 3878 not exposed | • no increased risk of major (OR=0.98; 95% CI 0.59-1.64) or minor malformations (OR=1.02; 95% CI 0.69-1.51) with prenatal SSRI exposure |
| Reis M and Kallen B., 2010   | Population-based, prospective cohort | SSRIs, bupropion, trazodone, SNRIs, TCAs, serotonin-2 antagonist reuptake inhibitors, MAOIs | 14,821 women with 15,017 infants with either early exposure, later exposure or both compared with 1,236,053 infants in the general population | • increased risk of general teratogenicity after exposure to fluoxetine (OR=1.31; 95% CI 0.85-2.02) and of cardiovascular defects after paroxetine exposure (OR=1.66; 95% CI 1.09-2.53)  
• risk of hypospadias with SSRI exposure (OR=1.30; 95% CI 0.94-1.80) and higher with paroxetine (OR=2.45); 95% CI 1.12-4.64)  
• TCAs (primarily clomipramine) associated with a higher risk of teratogenicity overall  
• risk of cystic kidney disease was elevated for SSRI (n=9) (OR=2.39; 95% CI 1.09-4.54) |
| Kallen BA, and Otterblad Clausson P., 2007 | Population-based, prospective cohort | citalopram, sertraline, fluoxetine, paroxetine | 6,555 infants exposed to first-trimester SSRI use | • increase in risk of heart defects and atrial and ventricular defects with paroxetine exposure  
• no overall increase in congenital malformations with SSRI exposure (AOR=0.89; 95% CI 0.79-1.07)  
• paroxetine was associated with an increased risk of ventricular and atrial septum defects (OR=1.81; 95% CI=0.96-3.09)  
• no association between craniosynostosis or omphalocele and maternal SSRI use |
| Einarson A, et al., 2008      | Prospective, cohort    | paroxetine                      | 3,379 infants with first-trimester paroxetine exposure vs. 1,174 unpublished cases vs. 2,061 infants from published databases vs. an unexposed cohort | • paroxetine is not associated with an increased risk of cardiovascular birth defects |

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant Studied</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einarson A, et al., 2009 (81).</td>
<td>Prospective, cohort</td>
<td>bupropion, citalopram, escitalopram, fluvoxamine, nefazodone, paroxetine, mirtazapine, fluoxetine, trazodone, venlafaxine, sertraline</td>
<td>928 women exposed to antidepressants in pregnancy vs. 928 controls</td>
<td>• prevalence of cardiac malformations was below the prevalence rate at 0.6%</td>
</tr>
<tr>
<td>Einarson A, et al., 2011 (82).</td>
<td>Prospective, cohort</td>
<td>bupropion, citalopram, fluvoxamine, nefazodone, paroxetine, mirtazapine, fluoxetine, trazodone, venlafaxine, sertraline</td>
<td>1243 with first trimester antidepressant exposure vs. 89 women exposed to &gt;1 antidepressant vs., 89 exposed to 1 antidepressant vs. 89 not exposed</td>
<td>• no association between antidepressant exposure and malformations</td>
</tr>
<tr>
<td>Klieger-Grossman, et al., 2011 (85).</td>
<td>Prospective, cohort</td>
<td>escitalopram</td>
<td>212 women exposed to citalopram vs. 212 exposed to other antidepressants vs. 212 exposed to non-teratogens</td>
<td>• escitalopram not associated with increased risk of major malformation</td>
</tr>
</tbody>
</table>
| Malm H, et al., 2011 (73). | Population-based, retrospective cohort | fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram               | 6,881 mother and child pairs with first trimester SSRI exposure vs. 618,727 mother and child pairs with no exposure | • overall major congenital abnormalities were not associated with SSRI exposure (AOR=1.08; 95% CI 0.96-1.22)  
• fluoxetine associated with increased risk of ventricular septal defects (AOR=2.03; 95% CI 1.28-3.21)  
• paroxetine associated with increased risk of ventricular outflow defects (AOR 4.68; 95% CI 1.48-14.74)  
• citalopram associated with neural tube defects (AOR=2.46; 95% CI 1.20-5.07) |
| Cole JA, et al., 2007 (66). | Case-control          | paroxetine as compared to all other antidepressants including SSRIs, SNRIs, TCAs, serotonin-2 antagonist reuptake inhibitors, MAOIs | 815 infants with exposure to paroxetine monotherapy vs. 1020 infants with mono- or polytherapy exposure vs. 4936 infants with other antidepressant mono- or polytherapy exposure vs. and a subset of 4198 infants with other antidepressant monotherapy exposure | • increased overall rate of malformations in infants after first-trimester paroxetine monotherapy exposure (AOR=1.89;95% CI 1.20-2.98), mono- or polytherapy (AOR=1.76;95% CI 1.18-2.64)  
• no increase in cardiovascular malformations with paroxetine monotherapy (AOR=1.46;95% CI 0.74-2.88) or for mono- or polytherapy (AOR=1.68;CI 0.95-2.97) |
<p>| Cole et al., 2007 (93) | Case-control          | bupropion compared to all other antidepressants including SSRIs, SNRIs, TCAs, serotonin-2 antagonist reuptake inhibitors, MAOIs | 1213 infants with first trimester bupropion exposure vs. 4743 infants with first trimester other antidepressant exposure vs. 1049 infants with bupropion exposure outside first trimester | • no increase in malformations with first trimester bupropion exposure |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant Studied</th>
<th>N</th>
<th>Findings</th>
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</thead>
</table>
| Louik C, et al., 2007 (62).  | Case-control                  | fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, venlafaxine, escitalopram, bupropion | 9,849 infants with malformations vs. 5,860 control infants | • SSRI use not associated with increased risk of cranosynostosis (OR=0.8; 95% CI 0.2-3.5) or omphalocoele (OR=1.4; 95% CI 0.4-4.5) or heart defects overall (OR=1.2; 95% CI 0.9-1.6)  
• sertraline associated with omphalocoele (OR=5.7; 95% CI 1.6-20.7) and septal defects (OR=2.0; 95% CI 1.2-4.0)  
• paroxetine associated with right ventricular outflow tract obstruction defects (OR=3.3; 95% CI 1.3-8.6) |
| Berard A, et al., 2007 (69). | Case-control                  | paroxetine compared to all other antidepressants including SSRIs, bupropion, trazodone, SNRIs, TCAs, sertotonin-2 antagonist reuptake inhibitors, MAOIs | 1,403 women with antidepressant exposure vs. infants without malformations | • no association between first trimester exposure to paroxetine (OR=1.38; 95% CI 0.49-3.92) or other SSRIs (OR=.89; 95% CI 0.28-2.84) and major congenital malformations  
• infants exposed to >25 mg of paroxetine had an increased risk of major congenital anomalies (AOR=2.23; 95% CI 1.19-4.17) or major cardiac malformations (AOR=3.07; 95% CI 1.00-9.42) |
| Alwan S, et al., 2007 (60).  | Population-based, case-control | citalopram, sertraline, fluoxetine, paroxetine                                         | 9,622 infants with major birth defects vs. 4,092 control infants | • SSRI use not associated with most congenital heart defects or other birth defects  
• SSRI use was associated with anencephaly (AOR = 2.4; 95% CI 1.1-5.1), cranosynostosis, (AOR=2.5; 95% CI 1.5-4.0) and omphalocoele (AOR=2.8, 95% CI 1.3-5.7) |
| Bakker MK, et al., 2010 (72). | Population-based, case-control | paroxetine                                                                               | 678 cases with heart defects vs. 615 controls | • increased OR for atrial septal defects (AOR=5.7; 95% CI 0.5-4.0), after preconception and/or first-trimester paroxetine exposure |
| Bakker MK, et al., 2010 (76). | Population-based, case-control | fluoxetine                                                                               | 4,255 infants, 178 of which were exposed to fluoxetine in the first trimester | • association between fluoxetine and infantile hypertrophic stenosis (1.7% infants exposed to fluoxetine vs. 0.2% non-exposed vs.infants with other malformations (AOR=9.8; 95% CI 1.5-62.0). |
| Ramos E, et al., 2008 (83).  | Retrospective case control     | SSRIs, TCAs, SNRIs, bupropion, mirtazapine, moclobemide, trazodone, nefazadone          | 2,329 women, of which 189 infants had major congenital malformation, vs. 2140 without malformation | • No association between antidepressant use in the first trimester and major congenital malformations (AOR=1.10; 95% 0.75-1.62)  
• no association between duration of antidepressant exposure and the prevalence of major congenital malformations  
• antidepressant class exposure was not associated with major congenital malformations |
| Wisner K, et al., 2009 (84). | Prospective, controlled observational | SSRIs                                                                                   | 238 women: 131 without SSRI exposure or MDD vs. 71 with partial or continuous SSRI exposure vs. partial or continuous MDD (n=36) | • no association between continuous nor first-trimester and minor or major malformations |
| Merlob P, et al., 2009 (61). | Prospective, controlled, observational | sertraline, fluvoxamine, fluoxetine, paroxetine, citalopram, escitalopram               | Congenital heart defects identified in 8 of 235 (3.4%) vs. congenital heart defects in 1083 of 67,636 (1.6%) non-exposed newborns | • SSRI exposure associated with two-fold increased risk of non-syndromic congenital heart malformations vs. 1.6% of non-exposed newborns (RR=2.17; 95% CI 1.07-4.39). |
## Study Design

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant Studied</th>
<th>N</th>
<th>Findings</th>
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</thead>
</table>
| Kornum JB, et al., 2010 (78). | Population-based prevalence study | sertraline, fluvoxamine, fluoxetine, paroxetine, citalopram, escitalopram | 2,062 of 216,042 women had SSRI prescriptions during early pregnancy | • SSRI exposure was associated with an overall increased risk of cardiac malformations (OR=1.7; 95% CI 1.1-2.5) and overall malformations (OR=1.3; 95% CI 1.1-1.6)  
• sertraline was associated with an increased risk of septal defects, 1.7% (n=6) (OR=3.3; 95% CI 1.5-7.5) |

Abbreviations: TCA=tricyclic; AOR=adjusted odds ratio; SSRI=selective serotonin reuptake inhibitor; RR=relative risk; aRR=adjusted relative risk; OR=odds ratio; CI= confidence interval; MAOI=monoamine oxidase inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor
Table II
Maternal use of antidepressants and the risk of post natal adaptation syndrome (PNAS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant studied</th>
<th>N</th>
<th>Findings</th>
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</thead>
</table>
| Chambers C.D., et al., 1996 (35). | Prospective, controlled | Fluoxetine            | 73 infants with third trimester antidepressant exposure vs. 101 infants with first and second trimester antidepressant exposure | • PNAS associated with late exposure only compared to early exposure (aRR = 8.7)  
• late pregnancy exposure associated with NICU admission (RR = 2.6) |
| Oberlander, T.F., et al., 2004 (104). | Prospective, controlled follow-up | Paroxetine, Fluoxetine, Sertraline or Citalopram alone or in combination with Clonazepam | 28 infants with late pregnancy SSRI exposure vs. 18 infants with SSRI and Clonazepam exposure vs. 23 non-exposed infants | • PNAS symptoms in 39% of infants with SSRI and Clonazepam exposure vs. 25% exposed to SSRI and 9% of controls (unadjusted RR = 3.5) |
| Costei, A.M., et al., 2002 (102). | Prospective, controlled | Paroxetine            | 55 with late exposure to Paroxetine, 27 infants with early exposure, and 27 with no exposure | • third trimester Paroxetine exposure was associated with PNAS symptoms in 22% of exposed compared to 11% controls (unadjusted RR = 4.0). |
| Zeskind, P.S. and L.E. Stephens., 2004 (156). | Prospective, controlled | Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine, Mianserin, Mirtazapine, Escitalopram | 17 SSRI-exposed vs. 17 non-exposed infants | • SSRI-exposed infants exhibited a wide range of neurobehavioral outcomes (p>0.05) |
| Laine, K., et al., 2003 (101). | Prospective, controlled, Fluoxetine | Citraolopram, Fluoxetine | 20 mothers and infants with late pregnancy antidepressant exposure vs. 20 mothers and infants without exposure | • exposed infants had lower Apgar scores and a 4-fold increase in serotonergic symptom score in first 4 days of life (P = .008)  
• as serotonergic symptoms increased, cord blood 5-H1AA levels decreased (P = .007) |
| Galbally, M., et al., 2009 (118). | Prospective, controlled | Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine, Mianserin, Mirtazapine, Escitalopram | 27 women exposed to medication vs matched controls | • third trimester antidepressant exposure associated with increased risk of PNAS, increased rate of admission to the special care nursery and higher rates of jaundice  
• no difference between specific antidepressants |
| Maschi, S., et al., 2008 (120). | Prospective, controlled | Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine | 200 neonates with antidepressant exposure vs. 1200 controls | • no association between antidepressant exposure and PNAS. |
| Levinson-Castiel, R., et al., 2006 (116). | Matched control | SSRIs Venlafaxine | 120 infants; 60 with prolonged antidepressant exposure vs. 60 controls | • PNAS occurred in 30% of infants with SSRI exposure vs. none in non-exposed group  
• 13% met criteria for severe neonatal dose-response effect. |
| Cohen, L.S., et al., (115). | Retrospective, cohort study | Fluoxetine            | 64 mother-infant pairs | • increased risk of special care nursery admissions after exposure to Fluoxetine in late trimester when compared to early trimester exposure (18.9% vs. 9.1%) |

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<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant studied</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Rampono, J., et al., 2009 (157). | Prospective, observational | fluoxetine, citalopram, paroxetine, sertraline, escitalopram, fluvoxamine | 56 mother-infant pairs; 27 exposed to SSRI vs. 11 to venlafaxine vs. 18 controls | • neonatal abstinence scores were higher (p > 0.05) on day 1 in exposed infants compared to controls.  
• exposed infants had higher serotonin scores and BNBAS scores for motor and autonomic clusters, habituation, and social-interactive (P<0.05) |
| Suri, R., et al., 2007 (44). | Prospective, naturalistic study | sertraline, fluoxetine, paroxetine, bupropion, nortriptyline | 90 women comprised of 49 with MDD taking antidepressant vs. 22 with MDD either not taking antidepressant or limited exposure vs. 19 healthy controls | • infants of women with MDD and exposed to antidepressants had greater rates of admission to the special care nursery than women with MDD who were not treated with antidepressants and healthy women (21%, 9%, 0% respectively) |
| Suri R, et al., 2011 (158). | Prospective, naturalistic study | sertraline, fluoxetine, paroxetine, bupropion, nortriptyline | 64 women; 33 with MDD and antidepressants vs. 16 with a history of MDD who were either not treated with antidepressant or had limited exposure vs. 15 healthy controls | • no differences between groups regarding Appgar scores, special nursery admissions or on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) |
| Hendrick V, et al., 2003 (55). | Prospective case series | fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, venlafaxine | 131 infants exposed to SSRIs | • 10.5% of infants exhibited PNAS. |
| Sit D, et al., 2011 (159). | Prospective case series | fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, venlafaxine | 21 mother-infant pairs with antidepressant exposure | • no association between cord-to-maternal concentration ratios and perinatal events |
| Ferreira, E., et al., 2007 (117). | Retrospective chart review | fluoxetine, citalopram, paroxetine, sertraline | 66 neonates with SSRI exposure vs. 90 without exposure | • behavioral signs in 77.6% of SSRI-exposed neonates compared to 41% non-exposed  
• tremors, agitation, spasms, hypotonia, irritability, sleep disturbances were reported in 63.2% of exposed infants and respiratory effects in 40.8%. |
| Kallen B., 2004 (40). | Prospective Swedish Birth Registry | paroxetine, fluoxetine, sertraline | 555 infants with late SSRI exposure vs. 728 controls | • increased risk for respiratory distress (OR = 2.21), hypoglycemia (OR = 1.62), convulsions (OR = 1.9) low appgar score (OR = 2.33) with maternal use of antidepressants  
• effects were not specific to any SSRI |
| Warburton, W., et al., 2010 (52). | Retrospective register study | fluoxetine, citalopram, paroxetine, sertraline | Infants exposed to antidepressants in the last 14 days of pregnancy vs. infants exposed earlier in pregnancy | • no difference in neonatal symptoms among women exposed to antidepressant in the last 14 days of pregnancy when compared to those who were not |
| Sanz EJ, et al., 2005 (100). | WHO database case series review | paroxetine, fluoxetine, sertraline | 93 infants with late SSRI exposure | • 69% of cases with neonatal behavioral symptoms were associated with paroxetine (n=64), 14 with fluoxetine, 9 with sertraline and 7 with citalopram |
## Table III
Maternal use of antidepressants and the risk of persistent pulmonary hypertension of the newborn (PPHN)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Antidepressant studied</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers CD, et al., 1996 (35).</td>
<td>Prospective observational cohort</td>
<td>fluoxetine</td>
<td>228 exposed women vs. 254 controls</td>
<td>• late in utero exposure associated with increased risk of PPHN as compared to first trimester exposure (2.7% vs. 0%)</td>
</tr>
<tr>
<td>Chambers CD, et al., 2006 (138).</td>
<td>Multi-center case control</td>
<td>citalopram, fluoxetine, paroxetine, sertraline, TCA, bupropion, venlafaxine, trazodone</td>
<td>377 women whose infants had PPHN vs. 836 matched controls</td>
<td>• after the 20th week of pregnancy antidepressant use was associated with PPHN (AOR = 6.1), but use of antidepressants prior to 20 weeks gestation was not</td>
</tr>
<tr>
<td>Kallen B. and Olausson PO, 2008 (139).</td>
<td>Population-based retrospective cohort</td>
<td>Citalopram, sertraline, fluoxetine, mirtazapine, paroxetine</td>
<td>504 infants with PPHN out of 831,324 births; 11 of which had antidepressant exposure</td>
<td>• early pregnancy SSRI use (RR=2.4) and late pregnancy use (after 34 weeks) (RR=3.6) associated with PPHN</td>
</tr>
<tr>
<td>Andrade SE, et al., 2009 (143).</td>
<td>Retrospective review</td>
<td>SSRI, TCA, miscellaneous</td>
<td>1104 exposed infants vs. 1104 matched controls</td>
<td>• prevalence of PPHN among infants with any third trimester antidepressant exposure = 1.81 per 1000 infants; no association among those infants exposed to SSRIs in third trimester (2.14 per 1000) vs. unexposed infants (2.72 per 1000)</td>
</tr>
<tr>
<td>Wichman CL, et al., 2009 (144).</td>
<td>Retrospective review</td>
<td>citalopram, venlafaxine, escitalopram, paroxetine, fluoxetine, sertraline, more than 1 SSRI</td>
<td>24,406 women with no SSRI use vs. 808 women with SSRI exposure</td>
<td>• 16 newborns diagnosed with PPHN but none of whom had exposure to SSRI (0.07% vs. 0.0% p&gt;0.99)</td>
</tr>
<tr>
<td>Wilson KL, et al., 2010 (160).</td>
<td>Prospective database case control</td>
<td>SSRI</td>
<td>11,923 births</td>
<td>• use of SSRIs in the second half of pregnancy was identified in 5% of the controls but none of the cases (OR=0)</td>
</tr>
<tr>
<td>Reis M and Kallen B., 2010 (41).</td>
<td>Population-based, prospective cohort</td>
<td>TCA, SSRIs, MAOIs, SNRIs (other antidepressant)</td>
<td>12,914 women with early exposure vs. 5,987 with later exposure vs. 4,080 with both early and late exposure vs. 1,062,190 women without exposure</td>
<td>• increased relative risk of PPHN for antidepressant exposure in early pregnancy (RR=2.30), for later exposure (RR=2.56) and for both early and later exposure (RR=3.44)</td>
</tr>
<tr>
<td>Kieler H et al., 2011 (142).</td>
<td>Population-based, prospective cohort; national health registers</td>
<td>SSRIs, other antidepressant</td>
<td>28,067 women filled a prescription for SSRI vs. 1,588,140 women without</td>
<td>• increased risk of PPHN for SSRI prescription in late pregnancy (AOR=2.1; 3 per 1000 liveborn infants compared with the background incidence of 1.2 per 1000) and before 8 weeks gestation (AOR=1.4)</td>
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<td></td>
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<td>• women without SSRI use and with prior hospitalization for a psychiatric disorder were at increased risk of having infant with PPHN (AOR=1.3)</td>
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<td>• women with a prior hospitalization for a psychiatric disorder and late gestation SSRI prescription were at greater risk (AOR=3.1)</td>
</tr>
</tbody>
</table>

Abbreviations: TCA=tricyclic; AOR=adjusted odds ratio; SSRI=selective serotonin reuptake inhibitor; RR=relative risk; OR=odds ratio; MAOI=monoamine oxidase inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor
### TABLE IV

#### Results Summary

**Teratogenicity**

- While individual studies suggest associations between SSRIs some specific major malformations, the findings are inconsistent, therefore the absolute risks appear small.
- SSRIs remain one of the best studied classes of medications used in pregnancy.
- Less data is available for SNRIs, mirtazapine, nefazadone, trazodone, and vilazodone.
- An increased risk of left outflow tract heart defects has been inconsistently demonstrated in association with bupropion.

**Postnatal Adaptation Syndrome (PNAS)**

- PNAS has been reported to occur in up to 30% of neonates exposed to antidepressants in late pregnancy and have most often been reported after exposure to paroxetine, fluoxetine, and venlafaxine.

**PPHN**

- The available evidence reports either a small association between PPHN and maternal antidepressant use during pregnancy or no association.
TABLE V

Clinical Points of Emphasis

- Unless there is a reason to use another class of antidepressant, SSRIs are generally considered first-line in pregnancy.
- A current response or history of a positive response to medication should help determine which medication to continue or initiate.
- Strongly consider using an antidepressant that the woman has responded to in the past, to avoid unnecessary exposures during pregnancy.
- Maximize non-medication evidence-based treatments.
- To avoid exposure to both illness and medication, use lowest possible dose while also avoiding under-treatment.
- Avoid polypharmacy with multiple psychotropic medications if possible.
- Tapering antidepressants in the third trimester has not been shown decrease the incidence of PNAS or improve infant outcomes and it carries the risk of precipitating relapse of depression.
- Exposure to untreated illness can be mitigated by preconception counseling, psychoeducation regarding risks and benefits of treatment and no treatment, close clinical monitoring, and a careful treatment plan tailored to the each woman.