Pharmacotherapy for Perinatal Depression

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Abstract: Perinatal depression is associated with serious risks for the mother, baby, and family. When considering treating perinatal depression with a drug indicated for the treatment of depression, the major concerns are whether the drug increases the risks of teratogenicity, pregnancy complications, poor neonatal adaptation, or neurodevelopmental disorders. Although different studies have produced different results, the majority have not shown increases in risk for selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, or the noradrenergic/dopaminergic drug bupropion. In this review we will discuss the reproductive safety data for these medications as well as monoamine oxidase inhibitors and benzodiazepines.

Key words: antidepressants, depression, pregnancy, perinatal, breastfeeding, teratogenicity, neonatal complications, neurodevelopment, autism

Key Points

(1) Perinatal depression poses serious risks to the mother, baby, and family.
(2) Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and bupropion are acceptably safe in pregnancy and lactation when used correctly, although double-blind placebo-controlled studies are lacking.
(3) Using neuroscience-based nomenclature rather than indication-based nomenclature helps destigmatize the treatment of perinatal depression.

Introduction

Perinatal depression is underdiagnosed and undertreated.† Affecting up to 12.9% of pregnant and postpartum women, depression is highly comorbid with anxiety disorders such as generalized anxiety disorder,
panic disorder, and obsessive compulsive disorder.\textsuperscript{2,3} The complications of perinatal depression include poor self-care, malnutrition, and noncompliance with prenatal care; higher rates of tobacco, alcohol, and recreational and illicit drug use; pregnancy complications including preterm birth; and impaired bonding to the baby, postpartum depression, lower rates of breastfeeding, marital discord, and poor parenting.\textsuperscript{4} Suicide in pregnant and postpartum women, usually by highly lethal means, is a leading cause of maternal death.\textsuperscript{5} Antenatal depression may also impair child neurodevelopment, independent of the effects of maternal or paternal postpartum depression.\textsuperscript{4}

Screening for perinatal depression is now considered standard.\textsuperscript{6,7} Additional screening for bipolar disorder and for anxiety disorders, though not yet standard, is important for clarifying diagnosis and treatment.\textsuperscript{8}

Although psychotherapy, including cognitive behavioral therapy and interpersonal psychotherapy, can be effective as a primary treatment for depression, medication is often necessary to achieve remission, especially in moderate to severe cases. Electroconvulsive therapy, also often combined with pharmacotherapy, is effective for severe depression, particularly with psychotic features, acute suicidality, or profound inability to care for self.\textsuperscript{9} In this paper we will review pharmacotherapy for perinatal depression.

The European College of Neuropsychopharmacology, in conjunction with other organizations, has introduced the use of neuroscience-based nomenclature in place of indication-based nomenclature to describe psychotropic medications.\textsuperscript{10} A free app, NBN2, summarizes the available information. Its use facilitates rational pharmacotherapy by focusing on the possible mechanisms of action (eg, affecting particular neurotransmitters, receptors, and enzymes). Using neuroscience-based nomenclature to describe the medication options to patients, their partners, and to colleagues, helps destigmatize the treatment of perinatal depression and enhance compliance. Both types of nomenclature will be used in this paper which reviews the use of SSRIs, SNRIs, TCAs, the noradrenergic/dopaminergic drug bupropion, monoamine oxidase inhibitors (MAOIs), and benzodiazepines. For a review of augmenting agents such as lithium and the medications typically referred to as antipsychotics, see Khan et al.\textsuperscript{11}

**Pharmacotherapy: Principles of Management**

Whenever a woman of reproductive age is given a medication, the reproductive safety profile should be considered, as 45% of pregnancies are unplanned.\textsuperscript{12} Up to 8.1% of women may use an antidepressant at some point in pregnancy.\textsuperscript{13}

The major concern is whether the drug increases the risks of birth defects (teratogenicity) over baseline. The background risk of birth defects worldwide is 3% to 6%.\textsuperscript{14} Other important concerns to be addressed are whether the drug increases the risks of pregnancy complications (eg, miscarriage, stillbirth, premature birth, intrauterine growth restriction), neonatal complications, or neurodevelopmental problems (neurobehavioral teratogenicity). The clinician must find a balance between the potential risks of medication and the known risks of illness to help the patient and her partner make an informed decision. Different patients will make different decisions regarding treatment, but even the patient who opts not to take medication should be monitored for clinical worsening to minimize the risks associated with illness.

If a patient is already on medication and doing well, in general the effective medication should be continued. When a patient decides to discontinue medication, a slow taper, preferably before she is pregnant, is preferred to abrupt discontinuation. For the pregnant patient who is presenting for care either with a recurrence or with new onset illness, the choice of medication will
be guided by individual and family history
and by the reproductive safety data.

In the setting of a constantly changing
physiological environment, dosage adjust-
ment is often needed during pregnancy to
maintain a therapeutic blood level and
again postpartum to avoid toxicity. Serum blood levels are not measured
routinely in the United States, therefore
clinical presentation will serve as the guide
to dose adjustments. If it turns out that the
patient was relatively undermedicated be-
fore pregnancy (ie, she appeared to be in
remission but actually had some subtle
residual symptoms that resolved with dos-
age increase during pregnancy), then the
increased dose may be well-tolerated post-
natally. Close monitoring postpartum is
important, given the high risk of relapse,
even on medication.

**Lactation**
The amount of medication transfer through
the breast milk is lower than the amount
transferred in pregnancy, therefore there is
no reason to switch from an effective and
well-tolerated medication to a different one
for breastfeeding. If the mother is psychia-
trically stable she may breastfeed, coordinat-
ing care with pediatrics. To attenuate the risk
of postpartum relapse, it is best to minimize
sleep deprivation by having someone else
care for the baby at night, either by giving
bottles of expressed milk or formula, or by
assisting the nursing mother so that she can
go back to sleep quickly.

The goal of treatment in the perinatal
period is to achieve and maintain euthy-
mic mood and to treat anxiety to remis-
sion. This goal will maximize the mother’s
ability to bond with and care for her baby,
both in utero and after birth, and mini-
mize distress, dysfunction, and disruption
for her and her family.

**Resources**
The majority of medications used to treat
unipolar depression are acceptably safe in
pregnancy and breastfeeding; we encourage
the reader to review the pregnancy and
lactation data for a given medication before
concluding that it cannot be used. Useful
resources include TERIS (http://depts.
washington.edu/terisdb), Reprotox (www.
reprotox.org), which is available for free
to trainees, MotherToBaby.org, Lactmed
(https://toxnet.nlm.nih.gov/newtoxnet/
lactmed.htm), and Briggs' Drugs in
Pregnancy and Lactation.18

**Human Pregnancy Reports**
Different studies have produced different
results for each of the major concerns. The
majority of reports showed no increase in
malformations, whereas some showed an
increase in one malformation or another.
The majority found no increase in the risk of
pregnancy complications (miscarriage, still-
birth, preeclampsia, or postpartum hemor-
rhage), though some showed small increases
in one complication or another. The majority
of studies have not shown an increase in
the risk of neurodevelopmental problems,
though some showed small increases. Much
of the literature examining the effects of
antidepressants in pregnancy relies on data
from large national registries, with the inher-
etent biases of retrospective population-based
studies. The discrepancies that exist in the
literature are often a result of differences in
study methodology, with many observa-
tional studies limited by heterogenous study
populations or control groups, use of pre-
scription databases as a proxy for medica-
tions taken, and failure to control for other
confounders. Although prospective double-
blind placebo-controlled trials would provide
the highest levels of evidence, such trials are
not yet available. The lack of consistency in
the findings prevents a conclusion of causa-
tion for any of these complications.

Studies that combine various medications
are less informative than studies of individual
medications. Nevertheless, composite studies
have been published and some will be
discussed when data for individual agents
are lacking. We will discuss a representative
sample of the available studies but encourage
the reader to review the literature in its entirety. Although meta-analyses may be a useful way to synthesize results from different types of studies, their findings may be limited by the failure to include all of the relevant studies and the disproportionate weight given to larger studies that may have discrepant findings but large sample sizes.

**Selective Serotonin Reuptake Inhibitors**

**Teratogenicity**

All of the SSRIs and their metabolites have been shown to cross the second and/or third trimester placenta. The risk of teratogenicity is primarily related to first trimester exposure, but pharmacokinetic data are lacking on transfer in the first trimester. Although there have been conflicting reports of associations between SSRIs as a group or between individual SSRIs and various malformations, no causal relationship has been shown. A Danish study compared women on SSRIs before conception who filled a prescription for an SSRI in the first trimester (continued use) with women who stopped taking an SSRI 3 months before pregnancy and then resumed after delivery (paused use).\textsuperscript{19} The study found an increased risk of cardiac malformation in both groups, compared with a control group of women without a diagnosis of depression or a history of filling a prescription for an SSRI. This study showed “confounding by indication,” meaning that the illness and related confounding factors rather than medication exposure likely account for the increased risk. Results for individual SSRIs differed, but the conclusion remained the same. Selected studies on fluoxetine, paroxetine, sertraline, and citalopram/escitalopram will be presented below.

**Fluoxetine**

A case-control study from the National Birth Defects Prevention Study found a statistically significant association between fluoxetine use and craniosynostosis with wide confidence intervals (CIs).\textsuperscript{20} A case-control study from the Sloane Epidemiology Center, in contrast, found no cases of craniosynostosis and found no increased odds ratio (OR) for total cardiac malformations or conotruncal defects, right or left ventricular outflow tract obstruction, or septal defects.\textsuperscript{21} Both studies were limited by the large number of comparisons. Given the differing findings, chance may account for the association. A Finnish medical birth registry study using prescription databases found an association between a fluoxetine prescription in pregnancy and isolated ventricular septal defects [adjusted odds ratio (aOR), 2.03; 95% CI, 1.28-3.21].\textsuperscript{22} However, the prevalence of fetal alcohol spectrum disorders was substantially higher in offspring exposed to SSRIs than in the control group, an example of confounds in women who take antidepressant medications. The Danish registry study found that filling a fluoxetine prescription in the first trimester was associated with an elevated aOR for total cardiac malformations (aOR, 2.05; 95% CI, 1.27-3.31) and atrial septal defects (aOR, 2.53; 95% CI, 1.2-5.32) compared with unexposed pregnancies.\textsuperscript{19} There was no dose-response relationship. Similar increases were found in the group that paused exposure during pregnancy. The authors concluded that the increased risks might have been due to confounding by indication. In a US Medicaid claims database study, after adjustment for maternal mental illness, no association was found between a prescription for fluoxetine in the first trimester and total cardiac malformations, ventricular septal defects, or right ventricular outflow tract obstruction (RVOTO).\textsuperscript{23} A Canadian study also using a prescription database found no increased risk of total or specific malformations following first trimester fluoxetine exposure after adjustment for maternal mental illness.\textsuperscript{24}
Sertraline
The National Birth Defects Prevention Study found a statistically significant association between anencephaly and sertraline exposure, with wide CIs.\textsuperscript{20} A case-control study from the Sloane Epidemiology Center, in contrast, found an increased OR with wide CIs for omphalocele, limb reduction defects, and anal atresia, but not central nervous system malformations.\textsuperscript{21} Both studies were limited by the large number of comparisons. Given the differing findings, chance may account for the association. The Danish registry study found no association with any of those 4 malformations.\textsuperscript{19} Filling a sertraline prescription in the first trimester increased the OR of atrial septal defects (aOR, 2.85; 95% CI, 1.35-5.99) and ventricular septal defects (aOR, 3.6; 95% CI, 1.86-6.96). Similar increases were found in the group that paused exposure during pregnancy. The authors’ conclusion was that the illness and potential confounders confer added risk. After adjustment for maternal mental illness, no association was found between a prescription of sertraline in the first trimester and any cardiac malformation, ventricular septal defects, or RVOTO in the US Medicaid claims database study.\textsuperscript{23} The Finnish registry study found no association between a sertraline prescription in pregnancy and any malformation, including heart defects.\textsuperscript{22} The prevalence of fetal alcohol spectrum disorders was substantially higher in offspring exposed to SSRIs than in the control group, highlighting the importance of confounding by indication. A Canadian insurance database study that compared the offspring of women who continued medication in the first trimester (based on prescriptions filled) to those of women who paused medication use, found no increased risk of total or specific malformations following first trimester sertraline exposure after adjustment for maternal mental illness.\textsuperscript{24} The authors noted that multiple comparisons may have accounted for the occasional positive associations found for some other antidepressants.

Paroxetine
The National Birth Defects Prevention Study found statistically significant associations between paroxetine exposure and omphalocele (aOR, 8.1; 95% CI, 3.1-20.8) and anencephaly (aOR, 5.1; 95% CI, 1.7-15.3).\textsuperscript{20} The authors reported significant associations with right ventricular outflow defects (aOR, 2.5; 95% CI, 1.0-6.0) and gastrochisis (aOR, 2.9; 95% CI, 1.0-8.4) but the 95% CI lower bound was 1.0, which means that the findings were not statistically significant. There was no association with septal defects. Multiple comparisons limited the strength of the conclusions. The Sloane Epidemiology Center Birth Defects Study also found an increased risk of right ventricular outflow defects (aOR, 3.3; 95% CI, 1.3-8.8), but not septal defects or other cardiac malformations.\textsuperscript{21} In both studies, lack of adjustment for multiple comparisons weakened the conclusions. The US Medicaid database study found no association between paroxetine exposure and total cardiac malformations, ventricular septal defects, or RVOTO after adjusting for maternal illness.\textsuperscript{23} A population-based cohort study using medical birth registers and prescription databases from Denmark, Finland, Iceland, Norway, and Sweden found that paroxetine exposure was not associated with total malformations, any cardiac malformation, or septal defects, but was associated with conotruncal and major arch anomalies (aOR, 2.27; 95% CI, 1.01-5.07) and RVOTOs (aOR, 2.54; 95% CI, 1.31-4.90).\textsuperscript{25} No adjustment was made for multiple testing or for confounding by indication. In a sibling-controlled analysis that combined SSRI exposures, there were no significant associations with any malformation, any cardiac malformation, or RVOTO. The Canadian insurance database study reported an association between paroxetine
exposure and septal defects (aOR, 1.39; 95% CI, 1.00-1.93) but this finding was not statistically significant.\textsuperscript{24} The 99% CI for total cardiac malformations was 0.87-2.03 (not significant), and as the authors acknowledged, multiple testing may have influenced the results.

Although the risks described in the studies above put paroxetine on par with any other SSRI, it has received increased scrutiny due to the findings of 2 unpublished industry-sponsored clinical trials that identified an increased risk of cardiac malformations, especially ventricular septal defects, which led the Food and Drug Administration (FDA) to issue a public health advisory regarding the risk.\textsuperscript{26} The pregnancy labeling was changed to category D from C (of note, this labeling system was replaced in 2015).\textsuperscript{27} In response to the labeling change, in 2008 the American College of Obstetricians and Gynecologists recommended that paroxetine be avoided in pregnancy, but the guidelines also noted that prescription of SSRIs should be individualized, and that if a woman did take paroxetine in pregnancy, fetal echocardiography could be considered.\textsuperscript{28} Given that a causal relationship between paroxetine and any malformations has not been established, we recommend that if paroxetine has been effective, it should be continued.

**Citalopram and Escitalopram**

Because citalopram and escitalopram give rise to the same active ingredients, we would expect the same effects to be reported. Discrepancies in the literature raise questions about the accuracy of the findings. The National Birth Defects Prevention Study reported an association between citalopram exposure and anencephaly, craniosynostosis, and omphalocele (OR, 4.0; 95% CI, 1.3-11.9).\textsuperscript{20} In contrast, the Sloane Epidemiology study reported no significant association between citalopram and any malformation.\textsuperscript{21} Escitalopram was not included in the analysis because there were too few exposures. The Danish registry study found a significant association between filling a prescription for citalopram and atrial septal defects (but ventricular septal defects) while no association was found between escitalopram and atroventricular septal defects.\textsuperscript{19} In the Finnish study, there was a significant association between neural tube defects and citalopram prescriptions (aOR, 2.46; 95% CI, 1.20-5.07), but not between escitalopram prescriptions and total malformations.\textsuperscript{22} This study did not adjust for drug, alcohol, or tobacco use and the rate of fetal alcohol syndrome was 10 times higher in SSRI-exposed pregnancies than in the unexposed control group. A British study found no statistically significant association between citalopram or escitalopram prescriptions and any malformations after controlling for maternal illness.\textsuperscript{29} In the Nordic study there was no statistically significant association between escitalopram (\(n = 3950\)) and total malformations or cardiac malformations.\textsuperscript{25} For citalopram (\(n = 11,193\)) there were 2 positive findings: for total malformations the aOR was 1.19 (95% CI, 1.07-1.31) and for RVOTO the aOR was 1.65 (95% CI, 1.10-2.48). No adjustment was made for confounding by indication or for multiple testing. The discrepancy between results for citalopram and escitalopram also calls into question the validity of the findings. The authors conducted a sibling-controlled analysis for all SSRIs combined (there were too few exposures to test individual agents) and found no increased risk for RVOTOs, cardiac malformations as a group, or total malformations, suggesting that confounding was responsible for the increased relative risks (RR) for particular malformations. A meta-analysis using data from congenital anomaly registries in Denmark, Wales, and Norway found a statistically significant association between first trimester exposure to citalopram (but not escitalopram) and severe congenital heart disease (OR, 2.09; 95% CI, 1.25-3.51) and hypospadias (OR, 1.69; 95% CI, 1.04-2.75).\textsuperscript{30} The study also found a statistically significant association.
between escitalopram exposure (but not citalopram) and abdominal wall defects as a group (OR, 3.52; 95% CI, 1.56-7.91); gastroschisis (OR, 3.95; 95% CI, 1.46-10.69), and clubfoot (OR, 2.18; 95% CI, 1.16-4.07). There were no significant associations with total malformations, total cardiac defects, or neural tube defects. The discrepancies between the findings call into question the validity of the findings. The analysis did not fully adjust for maternal illness, body mass index (BMI), other medications, drug, alcohol, or tobacco use, nor did it adjust for multiple testing. Another Canadian insurance database study reported that there was a significant association between citalopram exposure and total malformations (aOR, 1.36; 95% CI, 1.08-1.73), musculoskeletal defects (aOR, 1.92; 95% CI, 1.40-2.62), and craniosynostosis (aOR, 3.95; 95% CI, 2.08-7.52). There were no reported exposures to escitalopram. As the authors acknowledged, multiple testing may have influenced the results.

Pregnancy Complications
The majority of studies on SSRI exposure have found either no increased risk for adverse outcomes (such as spontaneous abortion, preeclampsia, postpartum hemorrhage, preterm delivery, low birth weight, and smallness for gestational age) or slightly increased risk estimates after adjustment for maternal illness severity. Different studies have adjusted for different potential confounders with varying degrees of success.

Pregnancy Loss
The rate of miscarriage in pregnancy is 30% in the first 6 weeks of gestation, including chemical pregnancies, decreasing to 15% by time of clinical recognition. The rate of stillbirth (pregnancy loss at 28 wk or later) is 1% for African American women and 0.5% for white women. Any consideration of medication effects on the rate of miscarriage must keep these baseline rates in mind. None of the studies looking at antidepressants and pregnancy loss has adequately controlled for potential confounding factors.

A Nordic study utilized data from various medical birth registers to examine whether SSRI exposure during pregnancy was associated with increased risks of stillbirth, neonatal death, and postneonatal death. On initial analysis, those who were exposed to SSRIs presented with higher rates of stillbirth and postneonatal death compared with unexposed women but the results were no longer statistically significant once adjusted for severity of maternal psychiatric disease.

Preeclampsia
A study using a US Medicaid database reported that there was no increase in the RR for preeclampsia with SSRI monotherapy (sertraline, fluoxetine, paroxetine, citalopram or escitalopram) or for bupropion in the fully adjusted model. In this study the comparison group was women with a diagnosis of depression and no antidepressant exposure. In the prospective population-based Norwegian MoBa study there was no association between SSRI exposure up to 34 weeks gestation and severe late onset preeclampsia after adjustment for anxiety or depression during pregnancy, although a trimester analysis was not possible.

Preterm Birth and Low Birth Weight
A 2013 meta-analysis examined the risk for various pregnancy and delivery outcomes associated with prenatal exposure to antidepressants. Although the study found statistically significant associations between in utero antidepressant exposure and gestational age, birth weight, and Apgar scores, the effects were small, with values in the exposed group generally falling within the normal range. The same meta-analysis found no significant association between antidepressant medication exposure and miscarriage. A meta-analysis including 8 studies examined the risk of preterm birth associated with SSRI exposure in pregnancy.
and concluded that women who received SSRIs during pregnancy had an increased risk for preterm birth compared with controls (aOR, 1.24; 95% CI, 1.09-1.41). Control groups included women with depression but without SSRI exposure and women without depression or medication exposure. In a subgroup analysis, the risk of preterm birth remained significant when comparing depressed women on an SSRI with depressed women treated with psychotherapy only (6.8% vs. 5.8%; OR, 1.17; 95% CI, 1.10-1.25). The risk seemed to be higher if the SSRIs were given in the third trimester compared with earlier exposure. In secondary outcome analyses neonates exposed in utero to SSRIs had higher rates of respiratory distress syndrome and significantly lower birth weight compared with the control group. The use of an unmedicated control group does not fully control for confounding by indication, thus limiting the strength of the conclusions. Another meta-analysis found an increased risk of preterm delivery in women taking antidepressants during the second and third trimesters.

Postpartum Hemorrhage
A study using a US Medicaid database found an increased risk for postpartum hemorrhage with SSRI use close to delivery after adjustment for maternal illness [adjusted RR (aRR), 1.42; 95% CI, 1.27-1.57]. A significant study limitation was the inability to control for alcohol, drug, and tobacco use or the use of over the counter medications.

Neonatal Complications
Transient neonatal complications, often referred to as poor neonatal adaptation syndrome, have been associated with SSRI and SNRI exposure. Whether these neonatal signs are related to drug exposure or to confounding factors has not been established. The complications most often described include mild respiratory difficulties, feeding disturbances, hypotonia or hypertonia, hypoglycemia, tremor, hyperreflexia, jitteriness, sleep disturbances, abnormal crying, and irritability. Symptoms start within 48 hours after birth and usually resolve within a few days to 2 weeks. The prevalence rates vary but have been reported to be as high as 30%. Symptoms usually resolve without intervention beyond supportive care, rarely requiring neonatal intensive care unit admission. One study found persistence of subtle signs at 1 month of age, but these were not clinically significant. Some important potential confounders in various studies included not controlling adequately for the use of other prescribed medications, over the counter medications, supplements, obstetric factors (cesarean section and preterm birth), maternal depression, nicotine, alcohol, marijuana and other illicit substance use, maternal obesity, or transgenerational effects of maternal stress. Using prescription databases as a proxy for actual medication exposure may result in misclassification of exposure. Another consideration is that different studies have used different rating scales, none of which were designed to assess the effects of antidepressant exposure, which makes comparison of results difficult. The signs have been attributed to toxicity (ie, side effects of medications persisting in the infant) and to a discontinuation (withdrawal) syndrome. A 2017 study reported that neonatal complications correlated with preterm birth rather than medication exposure or maternal depression. Additional studies are needed to clarify the nature of neonatal complications and their pathophysiology. In the meantime, since the publication of an FDA safety alert in 2004 regarding neonatal complications in the setting of SSRI or SNRI exposure, patients and clinicians often assume that medication should be discontinued in the third trimester. However, a large population-based study found no difference in the rates of transient neonatal complications between women who stayed on their medication through delivery and those who discontinued 2 weeks before delivery, after adjusting for maternal mental health.
illness. To stop medication in the third trimester would only increase the risk of relapse or exacerbation of the underlying depression and anxiety at a time of great vulnerability.

**Persistent Pulmonary Hypertension of the Newborn**

A 2006 study found a significant association between exposure to SSRIs (as a group) after the 20th week of pregnancy and persistent pulmonary hypertension of the newborn (PPHN) (aOR, 6.1; 95% CI, 2.2-16.8). The FDA issued a public health advisory about this association but retracted the warning in 2011 after the publication of conflicting reports, 1 positive and 3 negative. The FDA stated in 2011: “At present, FDA does not find sufficient evidence to conclude that SSRI use in pregnancy causes PPHN, and therefore recommends that health care providers treat depression during pregnancy as clinically appropriate.”

Subsequently, a 2012 multinational study reported an association between PPHN and filling 1 prescription for an SSRI during or after the 20th week of gestation when restricting the cohort to those with national subcodes for PPHN (aOR, 2.2; 95% CI, 1.2-3.9). In subgroup analyses of individual SSRIs, citalopram but not escitalopram was associated with an increased risk of PPHN (aOR, 2.3; 95% CI, 1.2-4.1) as were paroxetine (aOR, 2.8; 95% CI, 1.2-6.7) and sertraline (aOR, 2.3; 95% CI, 1.3-4.4) but not fluoxetine. The study included late preterm infants and was not able to adjust for confounding by indication, precluding assignment of causation. A 2015 Medicaid database study reported an increased risk for primary PPHN among term infants whose mothers had filled 1 prescription for an SSRI in the 90 days before delivery or to women who had filled at least 1 prescription after the 20th week of pregnancy, the association was no longer statistically significant. There were no significantly increased risks in any of these analyses for non-SSRIs combined [bupropion (N = 16,293), venlafaxine (N = 4629), desvenlafaxine (N = 69), and duloxetine (N = 772)]. Neither SSRI nor non-SSRI exposure was associated with an increased risk for severe PPHN, defined in this study as a “diagnosis of PPHN in the presence of a procedure code for respiratory assistance, extracorporeal membrane oxygenation, or inhaled nitric oxide therapy.” A 2017 study reported that SSRI exposure, defined as filling 1 prescription after the 20th week of gestation, was associated with an increased risk for PPHN (aOR, 4.29; 95% CI, 1.34-13.77), while venlafaxine exposure was not. In a supplemental table, the authors reported that they had enough cases to conclude that venlafaxine exposure in the first 20 weeks or throughout gestation was not associated with an increased risk, but not enough cases to assess the risk with use only after the 20th week, which contradicts the first statement. The supplemental table also indicated that when SSRI use occurred either only in the first 20 weeks or continuously throughout gestation there was no increased risk. This study did not adjust for major malformations or for use of folic acid, illicit drugs, alcohol, or tobacco, thus preventing conclusion of a causal relationship between SSRI exposure and PPHN.

**Neurodevelopmental Complications**

For many years there were limited data available on the potential long-term consequences of prenatal SSRI exposure on child neurodevelopment, though early reports suggested no impact on internalizing or externalizing behaviors. A 2017 population-based study investigated the association between prenatal SSRI exposure and childhood nonverbal cognition and compared these children with children who had been exposed to maternal depression but not to...
SSRIs. Children were assessed at ages 4 to 7 years. No association was found between prenatal SSRI exposure or untreated maternal depression and executive function at age 4, observed nonverbal intelligence at age 5, or neuropsychological function at age 7, after adjusting for maternal depressive symptoms prenatally and postnatally. In contrast, a study using the Finnish Medical Birth Registry found a small increased risk for a diagnosis code for speech/language disorders (aOR, 1.37; 95% CI, 1.11-1.70), but not for scholastic or motor disorders, when comparing offspring whose mother filled at least 2 prescriptions for an SSRI at any time in pregnancy with those whose mothers had a history of psychiatric illness but did not take SSRIs during pregnancy, after adjustment for other potential confounders. This study could not rule out confounding by indication.

**Autism Spectrum Disorders**

Autism spectrum disorders are thought to be due to genetic factors primarily with some contribution from environmental (antenatal) exposures. Among psychotropic medications, only valproic acid has been associated consistently with autism spectrum disorders. Nevertheless, concern was raised regarding SSRI exposure by the 2011 publication of a study that found an increased risk for autism spectrum disorders in offspring exposed to SSRIs (as a group) in the first trimester after adjustment for maternal illness (aOR, 3.8; 95% CI, 1.8-7.8). This study did not adjust for paternal mental health or for having an autistic sibling. Since then there have been a number of studies on exposure to antidepressants and autism spectrum disorders, the majority of which showed no increase in the risk of autism spectrum disorders after adjustment for potential confounders, while a small number showed increased risk. The lack of consistency in the findings prevents a conclusion of causation. Important factors to consider are how and when the autism spectrum disorder diagnosis was made, whether it was clinician confirmed, and whether the study adjusted for maternal and paternal psychiatric illness, sibling illness, concomitant medication exposures, and obstetric factors including delivery complications and preterm birth, among other potential confounders.

A 2017 study found no association between a diagnosis of autism spectrum disorders at 7 to 8 years of age and exposure to any SSRIs or other antidepressants, after adjustment for maternal and paternal psychiatric diagnoses. Another 2017 study found no increases in the risks of autism spectrum disorders or attention deficit hyperactivity disorder (ADHD) after adjusting for maternal and paternal health and performing a discordant sibling-controlled analysis. A 2017 study using propensity scoring to account for maternal mental illness severity found no significant association between filling a prescription for either an SSRI or an SNRI in pregnancy and autism spectrum disorders in the offspring. Results were consistent for SSRIs as a group, SNRIs as a group, and for individual SSRIs: citalopram, paroxetine, fluoxetine, and sertraline. In a sibling-controlled analysis (without propensity scoring) there was no significant association between SSRI exposure and autism spectrum disorders after adjustment for psychiatric diagnosis and alcohol or substance use disorder. When the nonuser group was separated into recent users (those who had filled any SSRI prescriptions within 1 year of pregnancy but not during pregnancy) and those who were remote users, the recent users were more likely to have offspring with autism spectrum disorders [adjusted hazard ratio (aHR), 1.85; 95% CI, 1.37-2.51]; neither group was exposed during pregnancy. In a subgroup analysis presented in the supplementary tables, SSRIs as a group were associated with autism spectrum disorders when the cohort was restricted to women with a diagnosis of a mood or anxiety disorder, comparing users with nonusers (aHR, 1.62; 95% CI, 1.04-2.52). In a trimester analysis in the mood and anxiety disorder
group, this association remained significant for second and third trimester use but not first trimester use. The authors pointed out that these secondary findings were likely due to confounding by indication.

Another 2017 study compared offspring outcome between women who took antidepressants during pregnancy and those who had a diagnosis of a psychiatric disorder but did not take antidepressants. In the primary analysis, the aOR for autism spectrum disorder without intellectual disability following exposure to SSRIs (as a group) was 1.57 (95% CI, 1.21-2.04). The association remained significant with propensity scoring (aOR, 1.76; 95% CI, 1.26-2.46). However, in a sibling-controlled analysis, restricted to siblings discordant for autism spectrum disorder, the association with SSRI exposure was no longer significant (aOR, 1.57; 95% CI, 0.92-2.66). There were no significant associations with autism spectrum disorders with intellectual disability in any of the analyses. Analyses for individual medications found increased ORs for citalopram (aOR, 1.75; 95% CI, 1.15-1.62), clomipramine (aOR, 2.07; 95% CI, 1.17-3.64), and venlafaxine (aOR, 2.41; 95% CI, 1.05-4.37) but not for paroxetine, sertraline, or fluoxetine. There were too few cases to conduct a sibling-controlled analysis or to adjust fully for the severity of maternal illness. Therefore, the positive findings for the individual agents may have been due to chance or residual confounding. Another 2017 study also found no association between SSRI exposure and intellectual disability after adjusting for maternal and paternal factors.

**Serotonin Norepinephrine Reuptake Inhibitors**

**Teratogenicity**
There is a substantial amount of data on venlafaxine, which is also applicable to desvenlafaxine, its active metabolite. There are fewer data on duloxetine. A Nordic population-based cohort study included outcome data on 2763 first trimester exposures to venlafaxine. There were no significant associations between exposure to venlafaxine and total malformations, total cardiac malformations, or septal heart defects after a sibling-controlled analysis and adjustment for other confounders. A 2016 meta-analysis of studies including venlafaxine (n = 3186) or duloxetine (n = 668) exposure concluded that there was no increased risk of total malformations. This meta-analysis did not include a 2014 Medicaid database study which also found that first trimester SNRI exposure (N = 6010, primarily venlafaxine) was not associated with an increased risk of cardiac malformations (RVOTO, ventricular septal defects, or other cardiac defects) in a depression-restricted analysis with propensity score stratification. A 2017 Canadian insurance database study reported a statistically significant association between venlafaxine exposure and respiratory malformations (aOR, 2.17; 95% CI, 1.07-4.38), a finding that had not been reported previously. The cohort was restricted to women who, in the year before pregnancy, had either a diagnosis of depression/anxiety or who had filled a prescription for an antidepressant. The study did not control for tobacco, alcohol, or illicit drug use, or for folic acid use, among other possible confounders, and the authors pointed out that the results may have been due to multiple testing.

**Pregnancy Complications**
There are fewer data for pregnancy complications in association with SNRI exposure than there are for SSRI exposure. Nevertheless, the same management principles apply. A Danish medical birth registry study reported an increased risk for miscarriage (defined as pregnancy loss up to 22 weeks’ gestation) in women with a hospital-based diagnosis of depression who filled at least 1 prescription at any time during the pregnancy for venlafaxine (unadjusted RR, 1.80; 95% CI, 1.19-2.72)
or duloxetine (unadjusted RR, 3.12; 95% CI, 1.55-6.31). The number of exposures was not specified. The study did not adjust for the trimester of use, alcohol, tobacco, or illicit drug use, or maternal illness. A study using a Canadian health insurance database reported an association between venlafaxine monotherapy exposure between 10 and 20 weeks gestation and preeclampsia compared with no exposure in women with a diagnosis of depression who had filled at least 1 prescription for venlafaxine (aRR, 1.95; 95% CI, 1.25-3.03). The results were adjusted for prescription for anticonvulsants, antipsychotics, and benzodiazepines but not for alcohol, or illicit drug or tobacco use, among other potential confounders, preventing a conclusion of a causal relationship.

A US Medicaid database study reported that venlafaxine exposure in mid-late pregnancy was associated with an increased risk for preeclampsia (aRR, 1.52; 95% CI, 1.28-1.83). Another study using the same database reported that venlafaxine exposure close to delivery was associated with postpartum hemorrhage after adjustment for depression severity and other potential confounders (aRR, 2.24; 95% CI, 1.69-2.97). Neither of these studies ruled out confounding by indication.

A study involving 52 patients exposed to venlafaxine, 5 to desvenlafaxine, and 14 to duloxetine after the 20th week of gestation found an increased risk for hypertensive disorders of pregnancy after adjusting for race, nulliparity, advanced maternal age, maternal obesity, and lifetime histories of cocaine dependence and panic disorder (aOR, 2.57; 95% CI, 1.34-4.9). This is a small study of a heterogenous group and further study would be needed to establish a causal relationship.

Neonatal and Neurobehavioral Neurodevelopmental Complications

SNRIs, similar to SSRIs, have been associated with transient neonatal complications which are often referred to as poor neonatal adaptation syndrome. The signs, which were described above in the section on SSRIs, likewise usually resolve spontaneously.

A prospective Canadian teratogen information service study evaluated the effects of in utero exposure to antidepressants on a child’s intelligence (IQ) and behavior. Children born to mothers taking venlafaxine in pregnancy (n = 62) were compared with children born to mothers taking SSRIs (n = 62); children born to untreated depressed mothers (n = 54); and children born to nondepressed mothers who were not taking medication (n = 62). Although maternal depression severity during pregnancy and at the time of testing predicted child behavior problems, antidepressant exposure during pregnancy was not associated with behavioral or cognitive impairments. Maternal IQ and the child’s sex—not antidepressant exposure—were predictive of a child’s IQ.

Tricyclic Antidepressants

TCAs include amitriptyline, nortriptyline, imipramine, desipramine, and clomipramine. Clomipramine acts as a serotonin reuptake inhibitor, whereas the others function more as norepinephrine reuptake inhibitors. Each also functions as an anticholinergic agent (among other effects) which accounts for some of the common side effects.

Teratogenicity

A 2010 Swedish Medical Birth Register study reported an association between TCAs and total malformations (aOR, 1.36; 95% CI, 1.07-1.72); cardiac malformations as a group (aOR, 1.63; 95% CI, 1.12-2.36), and ventricular septal defects and/or atrial septal defects (aOR, 1.84; 95% CI, 1.13-2.97). About 75% of the exposures were to clomipramine and about 25% were to amitriptyline. The results were adjusted for smoking and BMI but not for illness, illicit drug use, or other (non-antidepressant) medication, and the results may have been due to confounding by indication. In a depression-restricted analysis,
a study using a Medicaid database found no increased risk of cardiac defects among infants with first trimester exposure to TCAs (n = 5954). A 2017 Canadian study found an association between TCAs as a group and malformations of the face, neck, eye, or ear (aOR, 2.45; 95% CI, 1.05-5.72), as well as gastrointestinal malformations (aOR, 2.55; 95% CI, 1.4-4.66). The cohort was restricted to women who, in the year before pregnancy, had either a diagnosis of depression/anxiety or who had filled a prescription for an antidepressant. The study was unable to separate disparate malformations within larger categories and did not adjust for tobacco, alcohol, illicit drug use, or folic acid use, and the authors pointed out that the results may have been due to multiple testing.

Pregnancy Complications
A study using a Canadian health insurance database reported an association between TCA monotherapy exposure between 10 and 20 weeks gestation and preeclampsia, when compared with no exposure, in a cohort with a diagnosis of depression who had filled at least 1 prescription for a TCA (aRR, 3.23; 95% CI, 1.87-5.59). The results were adjusted for prescriptions for anticonvulsants, antipsychotics, and benzodiazepines but not for alcohol, illicit drug, or tobacco use. A 2013 study using the same database found no significant association between TCA exposure close to delivery and postpartum hemorrhage.

Neonatal and Neurodevelopmental Complications
In a Swedish Medical Birth Register study, the OR for first trimester TCA exposure in women with preterm birth was 2.36 (95% CI, 1.89-2.94). There was no increase in the risks of low birth weight or large/small for gestational age. The ORs for poor neonatal adaptation were increased: hypoglycemia (aOR, 1.83; 95% CI, 1.38-2.44); respiratory diagnoses (aOR, 2.50; 95% CI, 1.99-3.14); low Apgar score (aOR, 2.75; 95% CI, 1.91-3.96); central nervous system diagnoses (aOR, 2.92; 95% CI, 1.73-4.61); and jaundice (aOR, 1.39; 95% CI, 1.03-1.88). The results were adjusted for year of birth, maternal age, parity, smoking, and BMI but not for severity of maternal illness, tobacco, alcohol, or illicit drug use, or use of other medication. A 2002 prospective study compared children’s IQ, language, behavior, and temperament at 15 to 71 months after in utero exposure to TCAs (n = 46) or fluoxetine (n = 40) with a control group with what the authors considered to be nonteratogenic exposures (N = 36). No adverse neurobehavioral or cognitive effects were found in those children exposed to TCAs (or fluoxetine) during pregnancy. Untreated maternal depression, however, was negatively associated with IQ and language development.

Bupropion
Bupropion is a norepinephrine and dopamine reuptake inhibitor and releasing agent. A case-control study from the Slone Epidemiology Center reported an association between first trimester use of bupropion and ventricular septal defects (aOR, 2.5; 95% CI, 1.3-5.0). The results were adjusted for family history of birth defects and study center but not for maternal mental illness and may reflect unadjusted confounders. In contrast, a US Medicaid database study of 6691 first trimester bupropion exposures found no statistically significant risk for any cardiac malformation, ventricular septal defect, or RVOTO after adjustment for maternal illness. No other types of malformations have been associated with bupropion exposure. We were not able to locate published data on the risk of...
neonatal complications following bupropion exposure, other than a study that showed no increased risk for PPHN.55

Neurodevelopmental Complications
A multistate insurance claims database study found an association between bupropion but not SSRI exposure in the second trimester and ADHD in the offspring diagnosed at or before age 5.76 Both maternal and paternal psychiatric conditions were significantly associated with ADHD in the offspring. The study was not able to adjust fully for tobacco, alcohol, or drug use. The authors concluded that caregiver mental health should be taken into account when assessing and treating offspring with ADHD.

Monoamine Oxidase Inhibitors
Information on MAOIs (phenelzine, tranylcypromine, and selegiline) is limited to case reports. These drugs are usually avoided in pregnancy because of the potential for drug-food interactions, drug-drug interactions, and vasoconstrictive effects. Experimental animal studies do not suggest an increased risk of teratogenicity. If the patient has not responded to other medications or is already pregnant, consideration should be given to its continuation. We were not able to locate published reports of the use of phenelzine or tranylcypromine in breastfeeding. In a breastfed infant whose mother was using transdermal selegiline, infant serum levels were below the limit of detection at 12 days postpartum and development was normal at 5 months.77

Benzodiazepines
Benzodiazepines are GABA-A receptor agonists. Despite earlier controversy regarding an association between exposure to diazepam and chlor dia zepoxide and orofacial cleft, benzodiazepines have not been shown to increase the risk for total congenital malformations or specific malformations including orofacial cleft.29,78 Use in the third trimester may increase the risk for neonatal complications including poor muscle tone and hypothermia (floppy baby syndrome).78 The combination of benzodiazepine plus SSRI was associated with a higher risk of transient neonatal complications.44 We recommend using clonazepam or lorazepam, rather than diazepam or alprazolam, because of their intermediate half-life. Benzodiazepines are transferred to breast milk. In a case series of 124 breastfeeding women using primarily lorazepam, clonazepam, diazepam, and alprazolam, there were 2 reports of infant sedation but both were mild, transient, and involved multiple medications.79 As always, short-term benzodiazepine use is preferred, and chronic use should be reserved for situations where the benefits clearly outweigh the risk for the mother.

Pregnancy Registry Information
To gather additional information about medication safety, the National Pregnancy Registry for Psychiatric Medications has been established. Patients may enroll by contacting the registry at https://women smentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Conclusion
In this review we have highlighted the recent data on the reproductive safety of medications indicated for the treatment of depression. Medication selection should be based on individual and family history of response plus consideration of the reproductive safety data. The antidepressants (SSRIs, SNRIs, TCAs, and bupropion) and benzodiazepines discussed are acceptably safe in pregnancy and lactation when used appropriately. There are fewer data
for MAOIs but they may also be used when clinically indicated. Clinicians should review in detail the pregnancy and lactation data available before determining whether a drug may or may not be offered. Untreated illness poses serious risks to the mother, baby, and family, and these risks need to be weighed against the sometimes limited drug safety information. Clinicians considering the prescription of antidepressants should provide balanced information to their patients using neuroscience-based nomenclature that will help destigmatize the treatment of perinatal depression. With the benefit of knowing that the preponderance of evidence is reassuring regarding the safety of the basic antidepressant medications, patients may make educated decisions regarding their care and optimize their health outcomes.

References

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