Safety of Psychotropic Medications During Pregnancy

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KEYWORDS

• Perinatal reproductive psychiatry • Women's mental health • Pregnancy
• Psychopharmacology • Perinatal addiction

KEY POINTS

- Common psychiatric disorders during pregnancy and risks of no treatment in patients with moderate and severe disorder, including substance use disorders are reviewed.
- Selecting the best medications during pregnancy and the reproductive safety of psychotropic medications is discussed.
- Management of substance use disorders in pregnancy using medication-assisted treatments is explored.

INTRODUCTION

The objective of this article is to discuss the safety and efficacy of psychotropic medications during pregnancy. The common disorders and the risks of not receiving treatment of certain psychiatric conditions, including substance use disorders (SUDs), also are discussed.

Pregnancy is a time of stress. Stressing the nervous system—whether positive stress (eg, weddings and graduations) or negative stress, also referred to as distress

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(eg, loss of a loved one)—can precipitate psychiatric symptoms, especially in a mental health–vulnerable individual. Data show that pregnancy does not protect against relapse of symptoms in disorders, such as depression.[1]

Treatment recommendations for patients often are individualized. When developing a management plan, the provider should consider the patient's detailed psychiatric history: diagnostic work-up, previous treatment regimens that have failed, treatment modalities that have resulted in achieving euthymia (including past and current medication responses), current presentation, history of mental health during previous pregnancies, family history, social history, substance use history, and the timeline during which the course of treatment is proposed (whether or not the patient currently is pregnant or planning a pregnancy and so forth).

We will first start by reviewing common psychiatric disorders during pregnancy and risk of no treatment followed by a discussion of psychotropic medications in 6 drug categories as follows:

1. Considering psychopharmacology during pregnancy: common psychiatric disorders and risk of no treatment
2. Antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine uptake inhibitors (SNRIs), bupropion, and other antidepressants
3. Mood-stabilizing medications, including lithium, lamotrigine, valproic acid, other antiepileptic mood stabilizers, and antipsychotics as mood stabilizers
4. Antipsychotic medications, both typical antipsychotics and atypical antipsychotics
5. Anxiolytic/sedative hypnotic medications, including benzodiazepines, gabapentin, and other anxiolytics
6. Stimulants in pregnancy
7. Medication-assisted treatment (MAT) of SUDs, including opioid use disorders (OUDs), alcohol use disorder, smoking cessation, and cocaine/stimulant use disorder

If patient and provider decide to use pharmacologic treatment during pregnancy, efforts should be made to

- Select medications that have a well-studied reproductive safety profile. Ideally, all women of reproductive age should be continued on medication regimens that are safe in case of an unplanned pregnancy.
- Make modifications to medication regimens prior to pregnancy when possible, to confirm a stable and euthymic state on the new regimen prior to conception
- Limit the number of medication exposures to the fetus during pregnancy by maximizing 1 medication at effective doses instead of using multiple medications at lower doses.

In December 2014, the Food and Drug Administration (FDA) published the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, referred to as the Pregnancy and Lactation Labeling Rule.[2] This new system removes the previous letter categories—A, B, C, D, and X—as a means of determining medication safety for treatment of pregnant and lactating mothers. It requires a change to the content of the prescription drug labeling, which would now have to include up-to-date data to allow providers and mothers to make educated decisions.[2] As such, the following information aims to help providers guide patients in their decision-making process within the new and improved FDA guidelines.

Considering Psychopharmacology During Pregnancy: Common Psychiatric Disorders and Risk of No Treatment

When making considerations for treatment, variables to consider are severity of underlying disorder (during current episode and in the past), history of response to treatment, and patient preference and attitude toward treatment. The effect of maternal psychiatric illness (eg, depression) on fetal and neonatal well-being must be taken into account in the risk-benefit decision-making process with respect to use or choice to defer use of medication (ie, no treatment).[3–7]

Discontinuation of medication can be considered for people with a history of mild psychiatric illness. This change ideally should be done in conjunction with continuation or addition of nonpharmacologic treatments modalities.[8] In treatment of depression, for example, such modalities can include supportive therapy, cognitive-behavior therapy, or interpersonal therapy.[9–12]

Many women with history of depression who discontinue antidepressant medications during pregnancy may experience recurrent symptoms.[13] In a prospective study of 201 women, Cohen and colleagues[1] showed that patients who discontinued their antidepressants were 5 times more likely to relapse (rate of relapse of 68%) compared with women who maintained their antidepressants across pregnancy. This study also showed that 26% of women who continue antidepressants had a relapse of major depressive disorder during pregnancy.

Bipolar illness in pregnant patients carries a high risk of poor prenatal outcomes,[14,15] including but not limited to risk of self-harm, substance use, and poor compliance with prenatal care. Relapse rates in women with bipolar disorder are high in women who discontinue mood stabilizers proximate to conception (71% according to 1 study[15]).

Emergence of psychosis during pregnancy is an obstetric and psychiatric emergency. Psychosis could pose a risk to the mother and her infant. It can also hinder a patient's capability to participate in prenatal care or cooperate with care during delivery.[16,17]

More than 10% of women experience clinically significant symptoms of anxiety during pregnancy,[18] particularly during the first trimester. Pathologic anxiety has been correlated with a variety of poor obstetric outcomes, including increased rates of premature labor, low Apgar scores, and placental abruption.[19]

Many women with polysubstance use disorder are likely to attempt to abstain from using during pregnancy.[20] Continued use or relapse of SUD during pregnancy, however, can have devastating results.

Illicit opioid use is most prominent in the under-25 age group, which includes women of reproductive age. Withdrawal from opioids is known to cause premature labor, miscarriages, and fetal distress. There also is an increased risk for relapse, overdose, and death by patients who go through withdrawals.[21] In addition to OUD, alcohol use disorder (leading to fetal alcohol syndrome), cocaine/stimulant use disorder, nicotine use disorder, and other substances pose a danger to the health of young women of reproductive age and their fetuses during pregnancy.

Early screening, diagnosis, and intervention prior to and/or during pregnancy often reduce morbidity and mortality of mental health disorders for mothers and infants.

Pharmacologic treatment is usually recommended when nonpharmacologic strategies have not been efficacious and/or the risks of being psychiatrically ill during pregnancy might outweigh the benefits of nontreatment or the risks of fetal exposure to the medication.

Clinicians should attempt to make modifications to medication regimens prior to pregnancy to confirm a stable and euthymic state on the new regimen prior to

conception. The goal also should be to limit the number of medications exposures to infant during pregnancy. Maximizing 1 medication at affective doses is preferred to using more medications at lower doses.

Regardless of whether or not medication is used, vulnerable patients should be monitored closely because they are at a high risk for relapse during pregnancy and in the postpartum period.

ANTIDEPRESSANT MEDICATIONS

Risks Associated with Fetal Exposure to Antidepressant Medications

Most studies related to fetal risks associated with antidepressant use during pregnancy have been on SSRIs and tricyclic antidepressants (TCAs.) These studies have provided reassurance that SSRI medications, as a group, are not considered teratogenic[5,22,23]; however, research on the complete safety profile of these medications remains ongoing.

Although the relative safety of this class of medication with respect to fetal exposure has been reported,[24–26] other reports have described adverse perinatal outcomes, such as decreased gestational age, poor neonatal adaptation, and low birthweight. These studies are controversial, however, because other investigators have not observed the same associations.[27–29] Side effects, such as neurocognitive sequelae, are controversial at best, and further investigations are needed to determine if these are a direct result of antidepressants or of other confounders, such as parental ailment.[30–32]

A majority of reports studying the potential adverse outcomes of peripartum exposure to SSRI medications have been limited by nonsystematic assessment of infant outcomes, nonblinded raters, and small sample sizes. Most of such studies fail to assess the impact of other confounders, especially maternal depression or other psychiatric comorbidities, which by themselves can be associated with compromised perinatal outcomes.[33]

Neonatal adaptation is of some concern with antidepressant medications.[34] Symptoms include jitteriness, tachypnea, tremulousness, which usually are mild, are transient, and resolve without much medical intervention within the first few days of birth. It is important for pediatricians to be aware of infants' exposure and monitor them for supportive therapy.

Some studies have associated SSRI use in late pregnancy with persistent pulmonary hypertension of the newborn (PPHN), a serious and rare developmental lung condition. Chambers and colleagues[35] reported the risk of PPHN with exposure to SSRIs after 20 weeks at approximately 1%. Multiple large studies, however, have shown there is much lower risk of PPHN or no association at all between SSRI use and PPHN.[36,37] A large Medicaid database studied 3.8 million pregnancy outcomes and demonstrated that the risk of PPHN was 0.3% for women who were treated with SSRIs versus 0.2% among the nonexposed.[37] PPHN is correlated with multiple other risk factors that are not associated with SSRI use, such as cesarean delivery, race, and body mass index.[38]

There are fewer reports and sparse research conducted on the long-term sequelae of prenatal antidepressant exposure. In children (followed through early childhood), exposure to fluoxetine, venlafaxine, TCAs, or no medication has shown no differences in behavioral or cognitive development. These measures include IQ, language, temperament, behavior, reactivity, mood, distractibility, and activity level.[39,40] At least 1 study has shown no difference between children exposed to fluoxetine or TCAs during pregnancy and those not exposed in relation to the neurocognitive measures discussed preivously.[28,39]

Although some studies have reported that autism spectrum disorders, anxiety, and attention-deficit disorder (ADD) are more common in antidepressant-exposed children,[41] these studies do not account for many confounders, perhaps the most important of which is maternal psychiatric illness as a major contributing confounder.[42,43] The intuitive notion that the higher prevalence of these disorders is likely due to genetics or maternal illness is supported by studies that have controlled for variables, such as maternal psychiatric diagnosis and exposure to other medications.[44–47]

The data suggest that the risk of postpartum hemorrhage seems slightly increased in women taking serotonin reuptake inhibitors near the time of delivery.[48–50] Given the inconsistencies across findings on this topic and the small increase in risk observed in studies on this issue, there is no compelling evidence to change prescribing practices during pregnancy. Obstetricians, however, should be alert to the possibility of an increased risk of postpartum hemorrhage in this population, so that hemorrhage, should it occur, may be managed aggressively, with the goal of minimizing maternal morbidity.

Selective Serotonin Reuptake Inhibitor Medications: Sertraline, Fluoxetine, Citalopram, Escitalopram, Paroxetine, and Fluvoxamine

A large Medicaid data study (n = 949,504) by Huybrechts and colleagues[51] and another by Furu and colleagues[52] have concluded that SSRI (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram) exposure was not associated with an increased risk of any specific congenital malformations. This has also been shown in various other meta-analyses, which has been reassuring.[16]

Paroxetine is the 1 antidepressant, however, with previously concerning yet still controversial risks for fetal malformations. Reports have suggested that first-trimester exposure to paroxetine is correlated with an increased risk of cardiac malformations, such as atrial and ventricular septal defects.[53,54] Again, other peer-reviewed studies, including 2 independent, comprehensive meta-analysis studies, have not demonstrated the same increased risks of teratogenicity with first-trimester exposure to paroxetine.[55–58] Thus, although some still avoid paroxetine as first-line medication for an antidepressant-naive woman of reproductive age, this medication should surely be considered as a treatment option during pregnancy, given the previously noted reassuring data.

It has generally been assumed that the reproductive safety of escitalopram would be similar to that of the parent drug citalopram, because “S”-citalopram is 1 component of this racemic mixture. An observational multicenter prospective cohort study showed escitalopram does not seem associated with an increased risk for major malformations.[59] As seen in other studies of antidepressants, escitalopram was associated with higher rates of low birthweight (<2500 g). As is often seen in such studies, without a comparison group of women diagnosed with depression who are not taking an antidepressant, it is difficult to determine whether this adverse effect is due to the depression itself or exposure to the drug. This is particularly relevant given the multiple studies that have associated low birthweight with untreated depression and anxiety.

Fluvoxamine, a newer SSRI antidepressant, is FDA approved specifically for treatment of obsessive-compulsive disorder (OCD). Some patients who might not have responded to first-line antidepressant for the obsessive qualities of their anxiety may respond to this medication. Two large studies have shown no major congenital malformations in infants exposed to fluvoxamine compared with the unexposed infants.[52,60] The current data on fluvoxamine, however, is not as expansive of that of other antidepressants, simply due to the fact that it is not as widely prescribed.

Serotonin-Norepinephrine Uptake Inhibitor Medications: Duloxetine and Venlafaxine

Although there are fewer data on SNRI medications than on SSRI medications, so far these medications seem comparable in safety profile. A 2015 article, pooling data from 8 large cohort studies (3186 exposed to venlafaxine and 668 exposed to duloxetine), provides reassuring information regarding the reproductive safety of both venlafaxine and duloxetine after first-trimester exposure, concluding no association between exposure and increased risk of major congenital malformations.[61]

Currently, there are more data about the general safety of venlafaxine[52,62] compared with duloxetine. There is mounting evidence, however, for general safety of the latter during pregnancy. Despite some studies discussing possible association between duloxetine and increased risk of spontaneous abortion and poor neonatal adaptation syndrome,[63,64] causation is difficult and complicated to determine because it seems that having depression itself may have an impact on the risk of miscarriage.[65] Two prospective observational studies of safety of duloxetine can be combined to show that in 439 pregnancies, there were a total of 9 malformations (approximately 2.1%), which is comparable to the rate seen in the general population.

Gestational hypertension has been found significantly associated with the use of SNRI medications; thus, women on these medications should be monitored for hypertension. In a study of 686 women, gestational hypertension was significantly associated with the use of psychostimulants (odds ratio [OR] 6.11; 95% CI, 1.79–20.9) and SNRIs (OR 2.57; 95% CI, 1.34–4.93) after 20 weeks of gestation. Use of serotonin reuptake inhibitors was not associated with increased risk for hypertension. In women taking the SNRI venlafaxine or amphetamine stimulants, risk for gestational hypertension was seen more commonly at higher medication doses.[66]

Bupropion

There are data supporting the use of bupropion during pregnancy.[67–69] The Bupropion Pregnancy Registry concludes no major congenital malformation in association with this exposure in early pregnancy (n = 806).[67]

Although this information regarding the overall risk of malformation is reassuring, earlier reports had concerns of cardiac malformations in bupropion-exposed infants. To more carefully quantify this, a large insurance claims–based study was conducted. This retrospective cohort study, including more than 1200 infants exposed to bupropion during the first trimester, did not demonstrate an increased risk for cardiovascular malformations.[69]

Bupropion can be especially useful for patients with comorbid nicotine use disorder who are motivated to quit smoking and/or those with ADD (discussed later). Further studies are required to assess the risk of neonatal symptoms in bupropion-exposed infants and to better evaluate the long-term neurobehavioral effects of bupropion exposure.

Other Antidepressant Medications: Tricyclic Antidepressants, Mirtazapine, and Trazodone

TCAs, as a class, are not contraindicated for use during pregnancy. This class of medication, however, is not considered first line for treatment of mood and anxiety disorders due to generally increased and unwanted side effects (sedation, anticholinergic side effects, and so forth).[5,70,71] Desipramine and nortriptyline are preferred TCAs due to their less anticholinergic profile and less likely to exacerbate orthostatic hypotension during pregnancy.[72,73]

Data on the safety profile of mirtazapine for infants exposed in utero are considered limited (although reassuring)[6,74,75] and thus this medication should not be used as first-line treatment of mood or anxiety. Unlike typical SSRI medications, mirtazapine seems to have antiemetic properties[74] and has been used in case reports for treatment of hyperemesis gravidarum.[76] Given that hyperemesis gravidarum often is associated with significant anxiety, this medication may be a promising intervention for women with these comorbidities in the future.

The same is true for trazodone (often used as a sleep aid). Despite minimal reassuring data,[77] this medication should not use as first line for treatment of insomnia during pregnancy.

MOOD-STABILIZING MEDICATIONS

The 2 mood stabilizers most commonly considered during pregnancy are lithium and lamotrigine. Antipsychotic medications also play a major role in treatment of patients with manic-depressive disorder.

Lithium

The risk of prenatal exposure to lithium is notoriously coupled with fears of cardiovascular malformations (eg, Ebstein anomaly).[78] Previous reports have indicated that, although a signal for an increased risk of this cardiovascular malformation might be present, this risk is rare. In comparison to the general population, in which Ebstein anomaly occurs in 1/20,000 live births, lithium exposure in the first trimester was estimated to change this risk to at most 1/1000.[79] Despite approximately 50 years of data on this medication, new studies on the reproductive safety of this medication still continue.

A large retrospective cohort study of 1,325,563 pregnant women studied in utero exposure to lithium and risks of cardiovascular malformations.[80] This study, which included 663 women who used lithium during the first trimester of pregnancy, is the largest study of prenatal lithium exposure to date. Two comparison groups were women with no lithium exposure and women with bipolar disorder who used lamotrigine as a mood stabilizer. The findings of this study indicate a modest increase in the risk of cardiac malformations in infants with prenatal exposure to lithium. Compared with women with no known exposures, the relative risk of cardiac malformations calculated here was 1.65. Translating this into absolute risk, this means that if the risk of cardiovascular malformations is 1.15% in women with no exposure, the risk rises to approximately 1.90% in infants exposed to lithium. In this study, the risk of right ventricular outflow tract obstruction defects was 0.60 per 100 live births among infants exposed to lithium and 0.18 per 100 among unexposed infants.[80] The researchers also observed the increase in relative risk to be dose related. Such analysis, however, should be considered premature, considering lack of causation and possibility of other confounders.

Although the absolute risk discussed is not dramatic, this study confirms that lithium carries some teratogenic risk. Although the authors try to avoid prescribing teratogens during pregnancy, with lithium, at times, the benefits outweigh the risks.

Prenatal screening with fetal echocardiography and high-resolution ultrasound is recommended in patients who take lithium during pregnancy (approximately 16–18 weeks of gestation).[16]

Lamotrigine

Lamotrigine is another mood stabilizer used for treatment of bipolar disorder in pregnancy. This medication might not be as effective, however, as lithium in protecting

against manic symptoms and is usually used for patients with a history of bipolar traits or hypomania (ie, bipolar II disorder).

Earlier reports warned of possible increased risk of increased risk of cleft palate or cleft lip deformity in infants exposed to lamotrigine during the first trimester.[81] Multiple large studies have indicated that this risk is either nonexistent or very low.[82–84] In 1 study, researchers analyzed a total of 21 studies describing pregnancy outcomes and rates of congenital malformations. Compared with disease-matched controls (n = 1412) and healthy controls (n = 774,571), in utero exposure to lamotrigine monotherapy was not associated with an increased risk of major malformations. Rates of miscarriages, stillbirths, preterm deliveries, and small-for-gestational age neonates were similar in lamotrigine-exposed pregnancies compared with the general population.[85]

In short, lamotrigine is believed to be a relatively safe mood stabilizer for use during pregnancy.

Valproic Acid

Prenatal exposure to valproic acid is strongly associated with neural tube defects, such as spina bifida, and many other anomalies, including midface hypoplasia, congenital heart disease, cleft lip and/or cleft palate, growth retardation, and microcephaly, have been observed.[16,86]

In utero valproic acid has also exposure been associated other developmental neurocognitive deficiencies, including lower IQ and impaired cognition across several domains,[87] and increased risks of autism and ADDs later in childhood.[88,89]

As a general rule, women of reproductive age should not be prescribed valproic acid. If this agent is prescribed, patients should be fully educated on the risks profile of this medication, and robust contraceptive measures should be put in place. This medication ideally should be discontinued at least 6 months prior to planning for conception of any new pregnancy. This would allow for ample time to taper off the valproate, start a new medication, and ensure euthymia and mood stabilization on the new regimen.

Other Antiepileptic Mood-Stabilizing Medications

Information about the reproductive safety of other anticonvulsants, such as oxcarbazepine and topiramate is limited. These medications generally are not first line for the treatment of bipolar disorder, and therefore, ideally should be avoided during pregnancy. The same is true for carbamazepine, especially because prenatal exposure to this substance also has been associated with neural tube defects.[90] Teratogenicity is believed to increase with high maternal serum levels of anticonvulsant and exposure to more than 1 anticonvulsant.[16]

For patients exposed to anticonvulsants during pregnancy, neural tube defects should be evaluated with ultrasonography and maternal serum α-fetoprotein. Increase of folic acid supplementation (4 mg a day) prior to conception and during the first trimester is often recommended,[16] although the general efficacy of this intervention is not clear.

Antipsychotic Medications as Mood Stabilizers

Atypical antipsychotic drugs are commonly used in treatment of bipolar affective disorder (discussed later). Judicial use of adjunctive antipsychotic medication, or at times monotherapy, is common in patients with bipolar disorder. As-needed dosing of these medications (such as olanzapine or quetiapine) can be helpful in managing issues related to insomnia, anxiety, agitation, or irritability related to bipolar disorder.

ANTIPSYCHOTIC MEDICATIONS

Typical (First-Generation) Antipsychotics

Due to the long history of use of typical antipsychotics, there are considerable data available on the reproductive safety of these medications. There is no definitive association between typical antipsychotic exposure during pregnancy and risk of congenital malformations.[91,92] When using a typical antipsychotic, a high-potency neuroleptic (eg, haloperidol) should be used. Although lower-potency typical antipsychotics are not contraindicated, some historical data do exist for their increased risk of congenital malformations associated with prenatal exposure.[93]

Haloperidol, which has much historical data, is a good medication for use in medical settings, such as in florid psychosis during labor and delivery. This is especially true because this medication can be used intravenously, intramuscularly, and orally. The wide range of dosing of this drug also can facilitate improvement of symptoms and cooperation with care, improving safety of patient, safety of care providers, and delivery outcomes.[94]

Atypical (Second-Generation) Antipsychotics

The atypical (second-generation) antipsychotics medications currently serve multiple purposes in the treatment of mental health conditions. They also are used more frequently because they are associated with fewer side effects. In addition to treating psychotic disorders, such as schizophrenia, many are approved for treatment of bipolar disorder, and anxiety disorders. For this reason, this class of medication is perhaps the most multifunctional class of medication at the disposal of care providers.

The versatile use of these medications is important in pregnancy, because prescribers should try to minimize a fetus's exposure to multiple medications. Thus, a medication that could serve multiple purposes is of great value (eg, Seroquel for treatment of anxiety, insomnia, and psychosis.)

Although there are fewer data available on the reproductive safety of this class of medication, multiple large studies have shown that, as a class, they do not seem to have an association with any congenital malformations.[91,95–98]

One study concludes that prenatal exposure to quetiapine, aripiprazole, olanzapine, and ziprasidone does not increase the risk for congenital malformation or cardiac malformations. The possible exception noted is risperidone.[92] The data regarding the safety profile of risperidone are not easy to interpret. Another similar study on risperidone notes that data "should be interpreted with caution because no apparent biological mechanism can readily explain this outcome, and the possibility of a chance finding cannot be ruled out."[99] That said, even if we assume an increased risk is associated with the use of risperidone exists, the risk appears to be small.

Newer antipsychotics, such as lurasidone, iloperidone, and brexpiprazole, are under-represented in most large-scale studies, and more studies need to be done on their perinatal safety profile.

Pregnant patients on second-generation antipsychotics should be closely monitored and screened for gestational diabetes mellitus. Polypharmacy should be avoided to the extent possible to minimize the exposure to the fetus.

ANXIOLYTIC/SEDATIVE HYPNOTIC MEDICATIONS

Benzodiazepines

According to 1 study, 3.9% of American women with private insurance use a benzodiazepine during pregnancy.[100] First-trimester exposure to benzodiazepines has been reported to increase the risk for oral cleft formation for infants (estimated increase of

0.6%).[101] Other studies (including studies with pooled data analysis),[102–104] however, have not supported this association. Although some patients might avoid first-trimester exposure to benzodiazepines, this class of medication can be useful during the second and third trimesters, especially on an as-needed basis.

A 2018 prospective study compared 144 pregnancies exposed to benzodiazepines to a group of 650 unexposed. Infants exposed to benzodiazepines in utero were more likely to be admitted to a neonatal ICU (OR 2.02; 95% CI, 1.11–3.66) and to have a small head circumference (OR 3.89; 95% CI, 1.25–12.03) compared with unexposed infants. Other adverse effects, such as low birthweight, preterm birth, respiratory distress, and muscular symptoms, including hypotonia, were not observed.[105] This study did not find a significant increase in respiratory difficulties, as observed by Yonkers and colleagues.[106] There are reports of peripartum sedation, decreased muscle tone (floppiness), and breathing problems in some infants exposed to benzodiazepines.[107,108] In general, these symptoms appear infrequently and likely are more common in women who take high dosages of these medications.

The results of most benzodiazepine studies are challenging to analyze because in most cases of benzodiazepine exposure, women were also treated with other psychotropic medications. Some providers recommend tapering and discontinuing benzodiazepines around the time of parturition. This rationale is not fully supported, however, given the risk of puerperal worsening of anxiety disorders in women with a history of panic disorder and OCD.[109,110] In a case series, clonazepam-only use during pregnancy and labor did not cause any maternal or fetal compromise.[111]

For patients who conceive on benzodiazepines and do not wish to continue to take these medications over the course of their pregnancy, a gradual taper of these medications is required to prevent rebound anxiety, panic, insomnia, and serious withdrawal side effects, such as seizures. The slower the taper, the better it is tolerated.

Gabapentin

Gabapentin is used in a wide variety of clinical settings (epilepsy, pain management, restless leg syndrome, anxiety, and sleep disturbance); however, there is small amount of information available in regard to the reproductive safety of this medication,[112] and a greater number of exposed infants are required to definitively quantify the reproductive risk profile of this medication. One report reviews the accumulated data regarding the reproductive safety of gabapentin. Pooling all of the available data estimated the risk of malformation in gabapentin only–exposed infants to be less than that of the congenital malformations observed in the general population.[113]

Other Anxiolytics: Antipsychotics, Hydroxyzine, and Buspirone

Antipsychotic medications, such as Seroquel and olanzapine, can be used for as-needed treatment of anxiety (discussed previously). Hydroxyzine has limited but reassuring reproductive safety data.[114] Currently, no systematic data are available on the reproductive safety of buspirone.

STIMULANT MEDICATIONS AND PREGNANCY

Psychostimulants may be used for treatment of variety of reasons, including ADD, management of side effects (such as fatigue and cognitive deficits), enhancement of antidepressant medications, and treatment of narcolepsy.

A 2017 study has shown that infants exposed during pregnancy had increased risk for neonatal ICU admission, were more likely to have central nervous system–related disorders and were more often moderately preterm than nonexposed infants. There

was no increased risk for congenital malformations or perinatal death.[115] These findings are consistent with previous studies. What makes this study more useful and clinically relevant, however, is that it focuses on exposure to stimulants prescribed in standard doses as opposed to previous studies, which studied outcomes primarily in women who were abusing or misusing stimulants in combination with other substances.

Most of the studies that have focused on risk for major malformations have not demonstrated any increase in risk of major malformations with first-trimester exposure to methylphenidate. There are fewer available data on dextroamphetamine and amphetamine but still no evidence of teratogenesis.

Gestational hypertension also has been found significantly associated with the use of psychostimulants and seems dose-dependent.[66] Some studies of stimulants, including in women who abuse stimulants, have suggested higher rates of preterm birth, lower birthweight, and other adverse outcomes in infants exposed to stimulants during pregnancy.

The recommendations for use of these medications during pregnancy should be to try to taper off the medications, if feasible, or alternatively decrease the medication to the lowest possible dose and take it at the least number of times possible, on an as-needed basis. There are exceptions to this approach for patients who have challenged functionality if these medications are discontinued. Some examples include severe cases of attention-deficit/hyperactivity disorder (ADHD), leading to accidental injuries, such as car accidents, or cases of treating narcolepsy.

In some cases, bupropion, can be a consideration for replacement of stimulants during pregnancy. This can especially be useful for patients with comorbid depression and/or nicotine use disorder (discussed previously). Bupropion is also used by some providers (off table) for treatment of Attention Deficit Disorder.

MEDICATION-ASSISTED TREATMENT FOR SUBSTANCE USE DISORDERS

Opioid Maintenance Therapy: Methadone Versus Buprenorphine

Treatment with methadone had been considered the gold standard of care for patients requiring opioid maintenance therapy during pregnancy.[116,117] There is a growing body of evidence, however, that indicates buprenorphine should be considered equally efficacious or even as first-line therapy, especially due to its potential advantages for neonatal outcomes.[118,119] Often the decision to choose between these 2 agents is guided by patient history of use and treatment, preference, history of relapse, and need for closer monitoring.

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, an 8-site randomized, double blind, double-dummy, flexible-dosing, parallel-group clinical trial compared treatment with methadone to that of buprenorphine. The study showed that neonates exposed to buprenorphine required shorter hospital stays, lower morphine requirements, and an average of 4.1 days of treatment of neonatal adaptation syndrome compared with 9.9 days for the methadone group ($P<.01$).[119]

SUD is a disorder plagued by risk of relapse, which is a main concern of treatment with buprenorphine (a partial agonist) versus methadone (a full opioid agonist). Full agonists might leave patients with less cravings and lower risk of concomitant opioid use.[120] In the MOTHER study, 33% of women on buprenorphine therapy stopped treatment compared with 18% of the methadone group ($P = .02$).[119] In this study, however, women in both groups had to present to a

clinic daily. Buprenorphine in the outpatient setting can be prescribed on a monthly basis for patients in long-standing sustained remission, whereas most patients on methadone maintenance need to present to a specialized methadone clinic daily. As such, retention and compliance between the 2 can differ in the outpatient setting.

Special attention should be paid to the risk of polypharmacy with MAT for OUD for patients and their infants. When opiates were coadministered with psychotropic medications, the risk for neonatal drug withdrawal increased.[121] There also are increased risks for accidents, injuries, and respiratory depression for patients who use both opioids and benzodiazepines.[122,123]

Other Medication-Assisted Treatments for Opioid Use Disorder and Alcohol Use Disorder

Naltrexone is not a first-line treatment during pregnancy, especially for patients who are not on this medication prior to their pregnancy. For women who become pregnant while on treatment with naltrexone, this medication should be discontinued if the risk of relapse is low. In cases of high concern about relapse, risks, benefits, and alternatives should be discussed, including treatment with methadone or buprenorphine. Unfortunately, data on the safety profile of this medication are limited.[124]

Naltrexone is also used for treatment of alcohol use disorder. Other medications used for MAT for alcohol use disorder, including disulfiram and acamprosate, likely should be discontinued during pregnancy. The use of naloxone during pregnancy should be limited to cases of maternal overdose only to save a mother's life.

Medication-Assisted Treatments for Smoking Cessation in Pregnancy

The 3 MATs for nicotine use disorder for the general public are nicotine replacement therapy, bupropion, and varenicline. Data regarding the reproductive safety of nicotine replacement therapy are limited and controversial.[125] According to the American College of Obstetricians and Gynecologists recommendations, nicotine replacement therapy should be undertaken "only with close supervision and after careful consideration of the known risks of continued smoking versus the possible risks of nicotine replacement therapy."[126]

At this point, there is no information regarding the reproductive safety of varenicline; thus, it is generally not used in pregnancy.

In contrast, there are data to support the use of bupropion in pregnancy (discussed previously). This medication would be especially efficacious for patients with comorbid depression or ADHD requiring treatment with medications during pregnancy.

Cocaine/Stimulant Use Disorder In Pregnancy

Patients with a history of cocaine or stimulant dependence are at an increased risk for relapse of primary mood and anxiety disorders in addition to substance-induced mood disorder. Medications aimed at curbing cravings (such as topiramate and naltrexone) have been discussed. Patients with a history of cocaine dependence (with no current use) have an increased risk of hypertension. Thus, caution should be taken when prescribing SNRI medications to patients with current or remote history of cocaine use disorder with close observation for possible gestational hypertension.[66]

Best practices

What is the current best practice?

Psychopharmacology and pregnancy

- Screen, diagnose, and treat common mental health conditions prior to pregnancy when possible and/or otherwise during pregnancy
- Understand risks, benefits, alternatives, and appropriateness of psychopharmacologic treatment, including risk of no treatment
- Select medications that have a well-studied reproductive safety profile
- When possible, make modifications to medication regimens prior to pregnancy to confirm a stable and euthymic state on the new regimen prior to conception.
- Limit the number of medication exposures to infant during pregnancy.

What changes in current practice are likely to improve outcomes?

- Appropriate planning prior to pregnancy
- Early intervention prior to or during pregnancy or postpartum
- Continuous and close monitoring of symptoms
- Further research on safety and efficacy of medications during pregnancy

Major recommendations

- Screen all women of reproductive age for common mental health conditions, including, but not limited to, mood and anxiety disorders, OCD posttraumatic stress disorder (history of trauma past and present), ADHD, psychotic disorders (a medical emergency during pregnancy or postpartum), and SUDs.
- Treat women of reproductive age in need of psychiatric medications with medication that have a known favorable perinatal safety profile.
- Engage patients in conversations about family planning, including contraception, and adjust psychiatric medications before conception.
- Monitor patients during pregnancy and in the postpartum period for recurrence of symptoms, regardless of use of psychotropic medications.

Summary statement

Risks, benefits, alternatives, and appropriateness of psychotropic medications, including risks of no treatment, are discussed. Early screening, diagnosis, and intervention prior to and/or during pregnancy often reduce morbidity and mortality of mental health disorders.

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