

USE OF PSYCHIATRIC MEDICATIONS DURING PREGNANCY

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INTRODUCTION

Pregnancy confers no protection against psychopathology. To the contrary, during pregnancy, many women experience new-onset, continuing, or worsening psychiatric symptoms. Rates of depression are slightly higher among women who are pregnant than among those who are not. However, because of concerns about exposing the fetus to psychiatric medications, many women prefer to suffer through their symptoms during pregnancy rather than relieve their symptoms with medication. But these concerns must be weighed against increasing data showing that psychological symptoms in a pregnant woman can adversely affect the fetus. Here are a few examples. Women who experience depression during pregnancy are at risk for inadequate prenatal follow-up care, substance abuse, and smoking; they are more likely to seek an elective abortion; and the fetus is at risk for slower growth, low birth weight, and preterm birth (especially when the mother experiences anxiety in addition to depression). Additionally, several recent studies have reported that infants exposed prenatally to maternal depression and anxiety are more likely to exhibit attentional, emotional, sleep and behavioral problems later in childhood.

Women with nontreated schizophrenia and bipolar disorder are less likely to eat healthy foods and obtain prenatal care and are more likely to use illicit substances. Prospective studies of pregnant women with bipolar disorder have shown that relapse rates are much higher among nontreated than among treated women. Women with chronic mental illness have a high rate of losing their children to foster care. Fortunately, treatment of schizophrenia and bipolar disorder during pregnancy can help increase women's chances of remaining stable during pregnancy and of keeping their children.

Clinicians treating pregnant women should understand the risks and benefits for any medication they are considering prescribing and should clearly document their choices. In particular, clinicians should note in the medical records whether the patient is competent to consent to treatment and whether the patient's symptoms are improving with medication. If symptoms are not improving, there is little rationale for continuing to expose the fetus to the medication.

Clinicians should also discuss the baseline rate of birth defects with pregnant patients. These patients should be informed that 2%–4% of all infants are born with birth defects, regardless whether the mother took medication. This information will help patients understand that not every newborn baby will be perfect and that birth defects can occur even when the mother does everything possible during pregnancy to ensure her baby's health.

Of course, taking medication while pregnant can increase the risks for harm to the fetus, depending on the specific medication. To help clinicians choose which medications to prescribe for their pregnant patients, the US Food and Drug Administration has rated medications according to their risk for pregnant women and the unborn child. These are called the FDA use-in-pregnancy ratings, and the 5 categories are as follows:

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.

Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X: Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Although these ratings are useful, clinicians should bear in mind that they are mostly based on data from studies with animal subjects. Preferably, clinicians should base their treatment decisions on data from studies with human participants. Published data on human exposures should always take precedence over data on animal exposures. When such data are available, clinicians should document that their decision to prescribe a given medication for a pregnant woman is based on data from studies among humans.

During the next hour, we will discuss the various medications used to treat psychiatric illness and their effects on pregnant women and/or their unborn children. This discussion is divided into 3 sections, according to medication type: Section 1, Antidepressants; Section 2, Antipsychotics; and Section 3, Benzodiazepines. We will begin with antidepressants.

SECTION 1: ANTIDEPRESSANTS

The antidepressants that we will discuss are the selective serotonin re-uptake inhibitors, mood stabilizers, selective norepinephrine re-uptake inhibitors, serotonin–norepinephrine re-uptake inhibitors, a norepinephrine–dopamine re-uptake inhibitor, the tricyclics, and the newer tetracyclic antidepressants. We will begin this section by weighing the pros and cons of prescribing antidepressant medication for pregnant patients; then we will discuss some of the classes of antidepressants and the types of problems they can cause for the pregnant woman and her fetus and/or child. We will end with a brief discussion of what is known about the effects of a few miscellaneous antidepressants.

When weighing the pros and cons of prescribing antidepressant medication for pregnant patients, the answer to a major question must be known. That question is: To what extent are adverse outcomes the result of the depression as opposed to the result of the medication? This question has been the research objective for several studies. A large study in British Columbia compared infant outcomes among 3 groups of pregnant women: controls (mothers who were not depressed and did not take medication), depressed mothers who were not treated with selective serotonin re-uptake inhibitors (or any other medications), and depressed mothers who were treated with selective serotonin re-uptake inhibitors. The study found increased risk for preterm delivery and low birth-weight babies among women who were not treated and significantly higher risk among women who were treated. The specific percentages increased as follows: preterm births occurred among 5.9% of control mothers, 6.5% of nontreated mothers, and 9% of treated mothers; and low birth-weight babies were born to 7.4% of control mothers, 8.1% of nontreated mothers, and 8.5% of treated mothers. The biggest risk associated with fetal exposure to selective serotonin re-uptake inhibitors was respiratory distress, which occurred in newborns of 7.4% of control mothers, 7.8% of nontreated mothers, and 13.9% of treated mothers. These data show that although depression in a pregnant woman can increase the likelihood of some adverse outcomes, exposure to selective serotonin re-uptake inhibitors substantially increases that likelihood even more.

Because of the possible adverse effects just mentioned, whenever possible, clinicians should attempt nonpharmacologic options (such as individual, group, or couples counseling) before prescribing medication. Nevertheless, each case needs to be examined individually. For some women, the risk for harm from depressive symptoms (such as suicidality) clearly outweighs the risk for harm from antidepressant use.

When use of antidepressants is deemed to be beneficial, the likelihood of adverse outcomes can be minimized by keeping the medication at the lowest effective dose. One study compared adverse outcomes among pregnant women who received selective serotonin re-uptake inhibitors during pregnancy at high or at low-medium doses. A high dose was defined as twice the usual dose. Study results indicated that a higher dose was directly associated with lower gestational age at birth and greater chance of preterm birth. Specifically, the rates of preterm birth were 20% among those who took the high dose compared with only 9% among those who took the low-medium dose.

Now we will talk about the use of some specific classes of antidepressant medications in pregnant women, focusing on the types of adverse outcomes that can occur with each class.

Selective Serotonin Re-uptake Inhibitors

The effects of selective serotonin re-uptake inhibitors when taken during pregnancy have been studied to varying degrees. The types of adverse outcomes studied include birth defects, complications in the newborn, persistent pulmonary hypertension of the newborn, miscarriage, developmental complications of the child, and autism. We will discuss each outcome in more detail.

Birth Defects

According to most studies, increased risk for birth defects has not been linked with use of selective serotonin re-uptake inhibitors during the first trimester of pregnancy, with the exception of paroxetine. Therefore, whenever possible, paroxetine should be avoided during pregnancy. In April 2006, the Food and Drug Administration requested that the use-in-pregnancy rating of paroxetine be moved from category C (the category in which all other selective serotonin re-uptake inhibitors fall) to category D.

Complications in the Newborn

Several studies have reported complications in newborns who were exposed to selective serotonin re-uptake inhibitors during the third trimester of gestation. Reported incidence of these complications ranges from 15% to about 30%. Complications include respiratory distress, hypoglycemia, tremors, poor feeding, lower Apgar scores, and greater risk of needing admission to a neonatal intensive care unit. These complications can last up to 4 days after birth.

Persistent Pulmonary Hypertension of the Newborn

One adverse outcome that has recently received a great deal of attention is persistent pulmonary hypertension of the newborn (or PPHN). Some studies have found that risk for this outcome is greater after prenatal exposure to selective serotonin re-uptake inhibitors, especially during the second half of gestation. Characteristic of this condition is proliferation of smooth muscle cells in the pulmonary artery; and, notably, studies of rats have shown that exposure to fluoxetine leads to proliferation of these cells in the fetus. However, among studies of persistent pulmonary hypertension of the newborn, the numbers of studies with negative versus positive findings are about the same. The data might be confounded by the fact that many risk factors for delivering a child with this condition occur more commonly in women who are depressed. These risk factors include obesity, smoking, and reduced gestational age at birth. In January 2012, the Food and Drug Administration concluded that any evidence definitively linking pregnant women's use of selective serotonin re-uptake inhibitors with persistent pulmonary hypertension of the newborn was insufficient and that healthcare professionals should not alter their current practice of treating depression in pregnant women.

Miscarriage

Another potential adverse outcome resulting from antidepressant use by pregnant women is miscarriage. The baseline miscarriage rate of 7%–11% among nontreated women rises to 10%–16% among women who take a selective serotonin re-uptake inhibitor or a selective norepinephrine re-uptake inhibitor. However, studies of medications and risk for miscarriage have rarely considered confounding factors, such as parents' ages and physical health, use of nicotine and/or caffeine, and depressed mood.

Nevertheless, one case–control study did adjust for potential confounders and found that use of antidepressants by pregnant women was associated with a significantly increased risk for miscarriage (odds ratio 1.7). The highest risk was found for venlafaxine (odds ratio 2.1) and for the combined use of different antidepressants (odds ratio 3.5). Given these data, women who are at high risk for miscarriage should try to minimize use of antidepressants even while trying to conceive. Factors that would place them at risk for miscarriage include older age, history of miscarriage, chronic diseases (such as diabetes mellitus and lupus erythematosus), and recent delivery of another child.

Developmental Complications

Not many studies have examined developmental complications in children who were prenatally exposed to psychiatric medications. Pregnant women should be told about this lack of data. However, among the data that are available in the literature, some look reassuring. For example, some studies have compared internalizing behaviors (such as depression, anxiety, or withdrawal) and externalizing behaviors (such as impulsivity or behavior problems) among 4-year-old children. These studies found no difference in these behaviors among those children who were and were not prenatally exposed to selective serotonin re-uptake inhibitors. Of note, these studies did find a correlation between anxiety and depression in the mother and internalizing and externalizing behaviors in the children. A review of 15 studies showed that prenatal exposure to antidepressants did not affect children’s cognition or behavior; however, 2 of these studies reported significant differences in the children’s motor function (that is, they had less-developed fine motor skills).

Autism

Information about an association between prenatal exposure to selective serotonin re-uptake inhibitors and autism is limited. Positron-emission tomography studies have shown decreased serotonin activity in the frontal cortex of children with autism, and some authors have speculated that exposure to high levels of serotonin during early development might cause loss of serotonin terminals in the fetal brain. A study conducted by these authors reported that the risk for autism-spectrum disorders was 3.8-fold higher among children who had been exposed to selective serotonin re-uptake inhibitors during

the first trimester of gestation. More studies are urgently needed to examine the association, if any, between prenatal exposure to selective serotonin re-uptake inhibitors and autism. In the meantime, clinicians should continue to minimize fetal exposure to these medications whenever possible, especially during early gestation.

So far we have focused on the effects of selective serotonin re-uptake inhibitors. We will now move on to some of the mood stabilizers (specifically, lithium, valproate, carbamazepine, lamotrigine, and oxcarbazepine).

Mood Stabilizers

Lithium

Prenatal exposure to lithium is associated with the baby having an 8-fold increase in risk for cardiovascular defects. The best known defect is the Ebstein anomaly, a defect in which the tricuspid valve is displaced into the right ventricle. The baseline rate of children being born with this defect is one in 20,000. However, exposure to lithium during the first trimester of gestation is associated with a large (20- to 40-fold) increase from baseline. Also linked to lithium exposure are coarctation of the aorta and mitral atresia. Therefore, if a fetus has been exposed to lithium during the first trimester of gestation, the clinician should order ultrasonographic visualization of the fetal heart at weeks 18–20 of gestation.

Lithium also increases the risk for thyroid dysfunction in both the mother and the baby. Baseline thyroid levels should be obtained during the first trimester of pregnancy and every 3–6 months thereafter; at birth, the infant should be checked for thyroid abnormalities. Also at birth, the infant's lithium level should be checked, and even if this level is in the reference range, the infant should be checked for symptoms of lithium toxicity, which include low muscle tone, bradycardia, and abnormalities on electrocardiogram.

In pregnant women, lithium levels often drop as the pregnancy progresses and renal clearance increases. Therefore, lithium levels should be obtained at least monthly from the second trimester through the first month postpartum. If the lithium dose was

increased during pregnancy, it should be decreased immediately after delivery; otherwise, the mother's lithium levels can become toxic.

For children who were prenatally exposed to lithium, research is scarce. One small study compared the neurobehavioral outcomes of children exposed prenatally to lithium with those of their nonexposed siblings. No differences were found, but more systematic neurobehavioral studies remain to be done.

Lamotrigine

Compared with lithium, lamotrigine seems to be the safer choice for pregnant women. Data on several hundred prenatal exposures to lamotrigine have shown that the only reported adverse outcome has been an increased risk for cleft lip and cleft palate. Although the reported risks are inconsistent, the safest course is for pregnant women to avoid lamotrigine during gestational weeks 5–10, when the fetal lip and palate are forming. Another factor to keep in mind is that the high estrogen levels that occur during pregnancy will increase the blood clearance of lamotrigine; therefore, to maintain a therapeutic effect, a higher dose might be needed. In terms of effects on development of the child, a study of one-year-old infants who had been prenatally exposed to lamotrigine found no evidence of delayed development.

Valproate and Carbamazepine

These 2 antiepileptic medications are clearly teratogenic, most likely because of their antifolate properties. Folate is an important vitamin that women need to take during the first trimester of pregnancy to reduce the risk for neural tube defects in the fetus. As one would expect, valproate and carbamazepine have been associated with a significant increase in the risk for neural tube defects. Because the neural tube forms within the first 6 weeks of gestation, the risk from these medications occurs early in pregnancy. Supplementation with high doses of folate does not fully counter the risk of using these medications during the first trimester. Thus, before prescribing valproate or carbamazepine, clinicians should determine whether their patients are pregnant or are likely to become pregnant. They should ask female patients if they are using contraception and being regularly tested for pregnancy. Women who are unreliable about using contraception are not good candidates for these medications. All women of

reproductive age taking valproate or carbamazepine should be warned of the teratogenicity of these 2 medications. If the clinician learns that a patient has taken valproate or carbamazepine while pregnant, the clinician can order testing to determine whether a neural tube defect has occurred. Testing the patient's serum for alpha-fetoprotein level at 15–20 weeks of gestation will detect 75%–90% of neural tube defects, and ultrasonography at 18–20 weeks will detect more than 95% of neural tube defects.

In addition to increasing the risk for neural tube defects, valproate and carbamazepine also reportedly increase the risk for craniofacial defects, heart defects, and polydactyly. Valproate especially appears to increase an exposed child's risk for delayed development. Whenever possible, valproate and carbamazepine should be avoided throughout pregnancy

Oxcarbazepine

Too little is known about the safety of this medication in pregnant women. It is best that pregnant women avoid taking oxcarbazepine.

Other Antidepressants

Not enough data with regard to use of these other antidepressants in pregnant women are available for each class to be described separately.

Tricyclic antidepressants and one serotonin–norepinephrine re-uptake inhibitor, venlafaxine, have been linked with the complications of neonatal respiratory problems, low Apgar score, and hypoglycemia. However, similar to the selective serotonin re-uptake inhibitors, they have not been linked with an increased risk for birth defects. Tricyclic antidepressants can also be problematic for the pregnant woman because they can exacerbate common signs and symptoms experienced during pregnancy, such as orthostasis, constipation, and weight gain.

Exposure to bupropion, a norepinephrine–dopamine re-uptake inhibitor, has been linked with increased risk for spontaneous abortion.

Less is known about newer antidepressants such as mirtazapine (a tetracyclic antidepressant) and duloxetine (a serotonin–norepinephrine re-uptake inhibitor); thus, these medications are best avoided during pregnancy.

Dietary Supplementation with Natural Substances

For patients who show a partial response to antidepressants, one possible approach is to supplement the antidepressant with substances known to be safe in pregnant women, such as omega-3 fatty acids and folate (or folic acid).

Omega-3 fatty acids have helped some, but not all, patients with depression. For pregnant women, not only are omega-3 fatty acids safe, but they are even encouraged during pregnancy because they benefit fetal brain and eye development. Also encouraged are foods that are high in folate (such as spinach), not only for the healthful effects of folate but also because methylfolate controls a cofactor in the synthesis of the neurotransmitters serotonin, dopamine, and norepinephrine.

Antidepressants and Men

Although slightly off the topic of pregnancy, it is worth briefly mentioning the effects that antidepressants can have on male fertility. Compared with the research on the effects of antidepressant use in pregnant women, much less research has examined these effects in men. However, the research that has been conducted has indicated that antidepressants negatively affect male fertility. Some case reports have described an association between use of selective serotonin re-uptake inhibitors and decreased sperm motility and concentration; repeat analyses performed 1–3 months after discontinuation of these medications found that sperm concentration and motility improved markedly.

This concludes Section 1, Antidepressants. In summary, for pregnant women with depression, clinicians should attempt nonpharmacologic options (such as individual, group, or couples counseling) whenever possible, before turning to medications. When antidepressant medications are indicated, they should be prescribed at the lowest possible dose, for the shortest possible time. During the third trimester of pregnancy, the dose of antidepressant can be reduced to lower the risk for neonatal complications in the infant. However, this strategy can increase the risk for postpartum depression in the mother.

With regard to specific classes of antidepressants, the evidence so far shows that selective serotonin re-uptake inhibitors, with the possible exception of paroxetine, do not increase the risk for major birth defects. However, use of selective serotonin re-uptake inhibitors (as well as tricyclic acids and venlafaxine) during the third trimester of pregnancy is associated with a relatively high incidence of neonatal complications, especially respiratory distress. Valproate, lithium, and carbamazepine are known teratogens and should, whenever possible, be avoided during the first trimester of pregnancy.

All antidepressants, but especially venlafaxine and bupropion, should be considered to carry risks for miscarriage. The effects of antidepressants on birth weight and gestational age at birth remain uncertain. Until more data are available for newer antidepressants (such as mirtazapine and duloxetine), it is best that pregnant women not take them, if possible.

We now move on to discuss the effects of taking antipsychotics during pregnancy.

SECTION 2: ANTIPSYCHOTICS

The adverse effects that we will discuss with regard to antipsychotic medications are birth defects, extrapyramidal signs, and developmental complications. There is much less data on prenatal exposures to antipsychotic medications than to antidepressants, and additional adverse outcomes may emerge as the number of published exposures and studies grows. For example, no studies have examined rates of miscarriage following prenatal antipsychotic exposure. The question that was asked with regard to antidepressants—to what extent are adverse outcomes the result of the psychiatric condition, as opposed to the result of the medication?—could also apply to antipsychotics. This question arises partly because birth defects seem to be more common among children whose mothers have schizophrenia than in those whose mothers do not,

independent of in utero exposure to medication. Researchers need to account for this increased risk when designing studies.

In February 2011, the Food and Drug Administration updated drug labels for all antipsychotic drugs. The new drug labels now contain more information about the potential risks for abnormal muscle movements and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy. The specific risks are for abnormally increased or decreased muscle tone, tremor, sleepiness, difficulty breathing, and poor feeding.

We will now discuss the risks associated with taking first-generation or second-generation antipsychotics during pregnancy.

First-Generation (Typical) Antipsychotics

Studies looking for an association between haloperidol use and birth defects have produced mixed results. Although one study reported a slightly increased risk for limb defects among children exposed to haloperidol, other studies did not find an increased risk for birth defects among children exposed to haloperidol. Low-potency agents such as chlorpromazine have been linked with miscellaneous birth defects.

Infants who were exposed to antipsychotic drugs in utero should be examined at birth for extrapyramidal symptoms such as hypertonicity and tremors. Those who were exposed to low-potency agents sometimes have transient anticholinergic signs, such as tachycardia and urinary retention.

For pregnant women who need treatment for extrapyramidal symptoms, the best choice is the antihistamine diphenhydramine. For decades, diphenhydramine has been safely used by pregnant women.

In terms of developmental effects, one study looked for an association between development of children prenatally exposed to first-generation antipsychotics. Results indicated no difference in cognitive outcomes at age 4 among exposed and nonexposed children.

Second-Generation Antipsychotics

Data on exposure to second-generation antipsychotic drugs and birth defects are limited. However, these limited data indicate that second-generation antipsychotics do not seem to increase the risk for birth defects. Most published studies examined use of olanzapine, risperidone, and quetiapine, so it is best to use one of these drugs and to avoid those less-studied drugs such as aripiprazole, ziprasidone, clozapine, iloperidone, asenapine, and lurasidone.

Second-generation antipsychotics have been linked with a higher risk for gestational diabetes, so weight gain and blood sugar levels should be monitored closely for pregnant women who are taking these medications.

This concludes Section 3, Antipsychotics. In summary, the limited data seem to indicate a slight risk for birth defects among children prenatally exposed to first-generation antipsychotics but less risk among those exposed to second-generation antipsychotics. When antipsychotic medications are prescribed, they should be those for which we have the most data: olanzapine, risperidone, and quetiapine. Diphenhydramine is a safe treatment for extrapyramidal symptoms in pregnant women. Second-generation antipsychotics increase a pregnant woman's risk for gestational diabetes.

The last class of psychiatric medications that we will discuss is the benzodiazepines.

SECTION 3: BENZODIAZEPINES

As with the other classes of medications, data on use of benzodiazepines in pregnant women are limited. We will briefly discuss what is known about their effects on birth defects, sedation of the newborn, and developmental complications in the child. It is possible that additional adverse outcomes will be reported as the data continue to grow.

Some studies, but not all, have linked prenatal benzodiazepine exposure with an elevated risk for cleft lip in the child. Therefore, it is best to avoid benzodiazepines during weeks 5–10 of gestation, when the lip and palate are forming.

A more well-documented concern occurs when these medications are taken near term; benzodiazepine-exposed children can be born with sedation, hypotonia, and apnea. The best benzodiazepines to use during pregnancy are medium-acting agents with no active metabolites, such as lorazepam.

Another area for which data are limited, and/or conflicting, are developmental outcomes after prenatal exposure to benzodiazepines. One study reported motor and cognitive delays among children who were prenatally exposed to benzodiazepines, but other studies found no such delays. Until more studies are conducted, and unless the safety of benzodiazepines can be confirmed, use of benzodiazepines in pregnant women should be limited.

This concludes Section 3, Benzodiazepines. In summary, little data are available to support their safety or their risks. Until more data are available, benzodiazepines should be used in pregnant women only if clearly needed.

CONCLUSION

This concludes our overall discussion of the use of psychiatric medications during pregnancy. In summary, most of the data seem to involve the antidepressant selective serotonin re-uptake inhibitors. Of the 35,000 reports of fetal exposure to selective serotonin re-uptake inhibitors published so far, the evidence shows that these drugs do not increase the risk for major birth defects, with the possible exception of paroxetine. Other possible adverse outcomes that can result from use of antidepressants during pregnancy are neonatal complications, persistent pulmonary hypertension, miscarriage, developmental complications, and autism.

Valproate, lithium and carbamazepine are known teratogens and should be avoided in the first trimester of pregnancy whenever possible.

Second-generation antipsychotic medications are reasonable alternatives to these three mood disorder agents because the current data for their use during pregnancy look reassuring. Of these, most research has examined olanzapine, risperidone, and quetiapine.

Until more studies are conducted, use of benzodiazepines should be avoided by pregnant women; but if they are needed, the best choices are medium-acting agents with no active metabolites, such as lorazepam.

When reviewing the research, clinicians should give higher credence to data derived from studies among humans than studies among animals. Clinicians should also note whether confounding factors were accounted for and whether the risks for a given negative outcome occur with the mental illness alone, regardless of medication.

In general, medications should be prescribed at the lowest possible dose, for the least time necessary, and, whenever possible, clinicians should consider nonpharmacologic options for their pregnant patients.

When clinicians discuss treatment options with their patients, they should be sure to emphasize how little is known about the developmental outcomes of children who were prenatally exposed to psychiatric medications. However, when reviewing treatment options, clinicians and pregnant patients should also take into account the possible risks of not treating psychiatric illness.