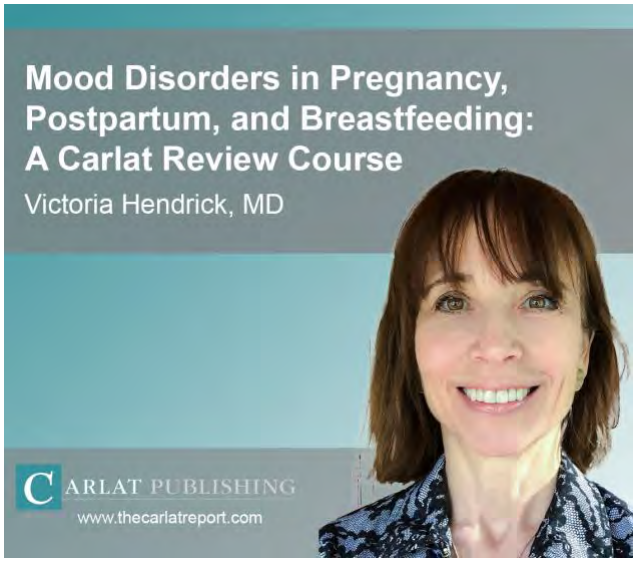
Module 3: Bipolar Disorder During Pregnancy and Postpartum

Webinar: Treatment of Bipolar Disorder in Pregnant and Postpartum Women

Transcript



Victoria Hendrick, MD, a clinical professor at the David Geffen School of Medicine at UCLA and is the director of inpatient psychiatry at Olive View—UCLA Medical Center, and Editor-in-Chief of The Carlat Hospital Psychiatry Report.

Dr. Hendrick has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

I'll be speaking about the treatment of bipolar disorder (BD) in pregnant and postpartum women. My name is Victoria Hendrick and I'm a clinical professor at the Department of Psychiatry at UCLA Medical Center and Editor in Chief of *The Carlat Hospital Psychiatry Report*. I have no conflicts or disclosures to report.

Today's learning objectives are to understand the course of bipolar disorder in pregnancy and the postpartum, to know the risks associated with pharmacologic treatments of bipolar disorder in pregnancy; to gain an awareness of the safety of psychiatric medications when taken during breastfeeding; and to summarize some of the current research findings in psychiatric treatment of bipolar disorder in pregnancy.

Preconception management
Ideally, we want to begin management at least six months prior to our patient's efforts at getting pregnant. That allows us time to ensure patients have prolonged stability preconception because they'll be less likely to relapse during pregnancy.

Preconception counseling also gives us time to switch to safer medications and to address any psychosocial stressors like conflict in a relationship or work stresses that could potentially destabilize a patient during pregnancy.

Course of bipolar disorder in pregnancy
Surprisingly, not much is known about this, but there are some data, including a recent study that I am summarizing here. Women were followed during pregnancy in the

postpartum, and what was found is that only about 5% of patients had relapses during pregnancy. Pregnancy seemed to be a fairly low risk time, thankfully, but a lot of patients relapsed in the postpartum.

This is consistent with what we see clinically. About one in three patients with BD will relapse in the postpartum. Women with an episode during pregnancy or the postpartum were less likely to have a second child. In fact, only about a third were likely to have a second child compared to women with an uneventful first pregnancy. If they had a second child, their risk of an episode was significantly elevated, around six times higher, after subsequent pregnancies compared to women who did not have any relapses in pregnancy or the postpartum. It's important for us to know how we can help these patients maintain stability, and if they want a second or third child, we can help them realize that this is an option for them. There are ways for us to help these patients remain stable during pregnancy and the postpartum.

Predictors of relapse
Red flags that help us identify which patients are most likely to have a relapse in an earlier onset of illness include:

- Abrupt discontinuation of meds
- Recent illness
- Earlier onset of illness
- History of multiple recurrences
- Rapid cycling
- History of suicide attempts
- Use of antidepressants
- Comorbid disorders

Potential impact of BD on pregnancy outcomes
Let me summarize the potential impact of BD on pregnancy outcomes. Women are more likely to use substances and to smoke. They're more likely to have low birth weight babies and preterm births. They're also more likely to contemplate suicide if they have a relapse of BD present and to inadequately follow up with prenatal care.

Lithium and pregnancy
What are the risks of lithium in pregnancy? The main risk is of Epstein's anomaly and other cardiovascular anomalies. Epstein's anomaly is a condition where the tricuspid valve is displaced into the right ventricle. It can be asymptomatic. Many people walk around every day who have this condition and don't even know they have it, or it can be fatal. It can vary substantially from one case to the next.

We worry about Epstein's anomaly in relation to lithium exposure in pregnant women and anybody else who takes lithium because it produces polyuria. I'm sure you see this with your patients on lithium. They need to urinate a lot. They experience diabetes insipidus and just like adults are experiencing this polyuria, the same thing happens to the fetus in utero. The fetus is experiencing polyhydramnios. This leads to excess amniotic fluid.

What is amniotic fluid? It's basically fetal urine. The fetus is bathed in amniotic fluid. It drinks this amniotic fluid, and when there's a lot of amniotic fluid, it's called polyhydramnios and it produces a lot of fluid load on the fetal heart. So the reason lithium is believed to affect the fetal heart is because of this excess amniotic fluid, this polyhydramnios putting all this pressure on the right ventricle of the fetal heart. The fetus is at risk of experiencing a number of cardiovascular defects related to polyhydramnios.

This is a very important point that I want to emphasize because I occasionally encounter papers that say the risk of Epstein's anomaly is really not so high related to lithium, and therefore we shouldn't be that worried, whereas in the general population, about one in 20,000 infants are born with Epstein's anomaly. For lithium exposed infants, it's about one in a thousand—20 times higher—but still would be very rare. But when you consider all the cardiovascular defects that can result from lithium exposure in addition to Epstein's, the risk becomes much more significant, more in the order of 5%.

We do need to be aware that lithium is a significant teratogen in the first trimester of pregnancy. If a patient has been taking lithium during the first trimester of pregnancy, you want to get a fetal echocardiogram between weeks 18 to 24. That's a time when the heart can be well visualized.

Thankfully, developmental outcomes appear normal. Children have been examined up to, I believe, about age five, and there haven't been any developmental outcomes that seem any different from unexposed children.

Risk of cardiac malformations

Now, regarding the risk of cardiac malformations secondary to lithium, there are things we can do about it. Let me tell you about this study that came out about five years ago. It was a large study of over a million pregnancies, and 663 infants were exposed to lithium. As you would expect, cardiac malformations were higher among the lithium-exposed infants—2.4 cardiac malformations per 100 live births among infants exposed to lithium versus 1.5 among nonexposed infants.

But the thing I found most interesting about this study was that the risk was dose related. So if the fetus was exposed to a daily dose of 600 mg or less, there was virtually no increase in risk of cardiovascular defects. For a dose of 600 to 900 mg, the risk was elevated—the risk ratio was 1.6; and then once the dose became higher, 900 mg or above, there was a tripling in the risk of a cardiovascular defect.

This goes to show that if we can keep the doses on the low end for our patients as much as possible, we can minimize the risk of adverse outcomes. This applies to any psychiatric medication, but it's rarely been studied with a level of detail as was done with lithium in this particular study.

Just to emphasize once more, the risk of lithium exposure in pregnancy, the risk of right ventricular obstruction, which encompasses Epstein's and any other cardiovascular defect in the right ventricle, you could see from this slide was 6% among lithium-exposed children versus 1.8% among unexposed children. This is again to emphasize that lithium exposure does increase the risk of cardiovascular defects in infants.

Lithium levels: pregnancy and postpartum
Some other points to keep in mind with lithium exposure is that lithium levels do appear to diminish over the course of pregnancy, presumably because of increased fluid volume. By the third trimester, they're about 34% lower than prepregnancy levels, so you might very well need to increase the dose over the course of pregnancy. I recommend getting blood levels of lithium at least monthly during pregnancy.

Keep in mind if you increase the dose during pregnancy, you must reduce it as soon as the baby is born because with the fluid loss, and with glomerular filtration rates normalizing following delivery, you could risk your patient becoming lithium toxic, so you want to make sure you bring the lithium back down to what it was prepregnancy as soon as the mother delivers. And make sure she's well hydrated because you don't want her to be dehydrated. That would increase the risk of lithium toxicity around delivery.

Stages of human development
I like showing this slide just to make the point that different medications are risky at different times in pregnancy. We can't say a medication is always risky throughout pregnancy, because in most cases the risk is to a specific organ that develops during specific times. For example, the heart forms primarily in the first eight to nine weeks of pregnancy. Beyond that, there's not going to be as much risk to the formation of the heart because the heart will have already formed.

We worry, for example, with benzodiazepines and cleft lip and cleft palate, since at least some studies have shown that potential risk, and the lip and palate form around weeks 6 to 10. Using benzodiazepines after that period of time would be linked with a much lower risk. You can use medications judiciously, just keeping these points in mind.

Antiepileptic drugs in pregnancy
Valproate and carbamazepine are associated with substantial risks of neural tube defects. The risk of neural tube defects, unfortunately, is very early, even before women realize they're pregnant. The first six weeks of pregnancy, the first 42 days is when the neural tube forms. If your patient tells you or finds out she's pregnant four weeks into the pregnancy, the harm may very well be done. The neural tube defect could very well have already occurred.

It's important when you have patients on valproate or carbamazepine to not prescribe these medications to patients who you can't trust are using contraception reliably. Be very careful who you prescribe these medications to women of reproductive age. Other risks of these antiepileptic drugs are cranial defects and polydactyly, which refers to extra digits in the hands and feet.

Prenatal valproate is particularly a concern. It's associated with poor school performance, lower IQ, and even autism. I do worry about these medications.

Mechanisms of AED-mediated teratogenesis
The reason for these risks are believed to be from their antifolate activity, which is through these mechanisms I list on the slide. Some people have thought, well how about if we bombard our patients with high doses of folate, much higher than they would normally get in a prenatal vitamin? But that has not been found unfortunately to reliably prevent the risk of neural tube defects.

Valproate in France and the UK
Because of these concerns, especially about valproate, you see other countries taking steps that I believe we should be taking in the United States. For example, France has a partial ban on the prescription of valproate for women and girls unless they're using a form of contraception.

In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHR) (which is like our FDA) bans valproate for all women of childbearing age, unless they're in a pregnancy prevention program where they acknowledge the risk of valproic acid in pregnancy, agree to use contraception, and take pregnancy tests regularly during treatment.

This program is similar to what's done for Accutane. If any of you have had teenage kids that have ever taken Accutane, you are familiar with the programs that we have in the United States to make sure patients don't get pregnant on highly teratogenic medications like Accutane, we should be doing the same thing for valproic acid.

Lamotrigine in pregnancy
Lamotrigine does not appear to increase the risk of birth defects, and it appears effective against relapses to manic and depressive episodes in pregnancy. I'll talk about some studies that have looked at lamotrigine in pregnant women with BD.

But first let me just tell you lamotrigine clearance does increase a lot in pregnant women. We know estrogen increases the breakdown of lamotrigine, and by the time women reach the third trimester, clearance of lamotrigine can increase by up to 250%. You very well might need to increase the dose during pregnancy and then just remember to reduce it after delivery.

Here was a study that looked at women who had continued lamotrigine versus women who discontinued mood stabilizers during pregnancy (all mood stabilizers, lamotrigine, or any other mood stabilizer). Most of the women who discontinued mood stabilizers did so rapidly. I will point out that when a patient discontinues a medication abruptly, that does increase the risk of relapse to BD, so we always advise our patients—pregnant or not—at any time in their lives, to discontinue mood stabilizers gradually, at least over the course of two weeks, if not longer. Nevertheless, the study found that the women on lamotrigine had a risk of 30% of relapse during pregnancy versus a 100% among the women who discontinued mood stabilizers. It shows that lamotrigine did seem to protect women

against relapse, and if that's the case, it gives us an option in addition to lithium valproic acid and carbamazepine that might be safer for our pregnant patients.

Second-generation antipsychotics
There's some data on the risks of second-generation antipsychotic medications (SGAs). I will say it's harder to study antipsychotics than other medications because in general, women with psychotic illnesses do not tend to stay in research studies as reliably as other patients, so they're often lost to follow-up.

But we do have some data. This paper found twice the rate of major congenital defects among any psychotic-exposed infants versus controls, but there was no specific pattern of malformation, and no specific drug was linked with the birth defects. This suggests that it was the underlying illness or unidentified confounds that explain this excess risk of birth defects.

We worry if we always see the same birth defect, for example, with a certain medication, you always see a certain birth defect (eg, a cardiovascular defect or a cleft palate). But when birth defects are all over the place, then you become a little more skeptical that it's a drug risk and you want to look at other reasons for this excess risk of defects.

Antipsychotic use in pregnancy
This was another study done by a group that often publishes on antipsychotics in pregnancy. In fact, just recently, they had another paper that came out on antipsychotics in pregnancy. They found in this study no increased risk of birth defects with the exception of risperidone, where there was 26% increased risk in cardiac malformations.

You can see these were fairly large numbers of exposure, so that was reassuring with quetiapine having the largest number of exposures. Even if we don't worry about birth defects, we do worry about other concerns. Babies have been born with extrapyramidal symptoms, sleepiness, and jitteriness. We want to keep the doses as low as possible for our patients to try to minimize these potential adverse equality in the infants.

What do we make of this elevated risk of cardiovascular malformations with risperidone? When you see an elevated risk of a certain medication, we want to see if it's being found in other studies ,and for risperidone that hasn't been found. In other studies of pregnant women. Nevertheless, if you have other choices besides risperidone, it's makes sense to try to go with some other medication until we have more data on risperidone in pregnancy.

Placental passage of antipsychotic medications
Quetiapine has been a popular medication for pregnant patients who require antipsychotic medications, in part because we have so many data on it as I showed earlier, and also because of this study that's found that the placental passage seemed the lowest for quetiapine. This was done with studies where the researcher obtains some umbilical cord blood and looks at basically how much was getting into the fetus versus how much was in the mothers. Quetiapine looked the like the least was getting into the fetus.

We do use haloperidol and olanzapine, even though they have higher placental passage ratios, just because there are a lot of data. These medications have been around a long time

and there don't appear to be any adverse sequelae linked with these medications. They are also frequently used in patients requiring antipsychotic medications in pregnancy.

Prenatal exposures to SGAs
What about newer antipsychotics? Unfortunately, there's very little data on paliperidone (Invega); asenapine (Saphris); iloperidone (Fanapt); lurasidone (Latuda); and clozapine (Clozaril).

For any of these, I'd say be careful with lurasidone and clozapine because I have encountered clinicians who will literally take a patient off, say quetiapine or haloperidol, and place her on lurasidone or clozapine because lurasidone and clozapine are listed Category B in pregnancy, whereas other antipsychotics are listed Category C.

Old FDA Use-in-Pregnancy categories
In fact, I will say some drug company reps have even touted the Category B rating as an advantage of their medications, and that is very misleading.

A: Controlled studies in women show no risk

B: Animal studies show no risk but there are no controlled studies in humans, or animal studies show adverse effect that has not been confirmed in human studies

C: Animal studies show risk but there are no controlled studies in humans, or studies in animals and humans are not available

D: There is evidence of risk in humans, but the drug may have benefits that outweigh the risk

X: Risk outweighs any benefit

Let me explain why. Category B (above) is for animal studies showing no risk, but there are no control studies in humans or animal studies show an adverse effect that has not been confirmed in human studies. The key sentence here is **there are no control studies in humans**, so a medication could be listed as Category B just because there are animal studies.

As you might be aware, thalidomide looked fine in rabbits, and it wasn't until humans began taking thalidomide, we realized how dangerous it was. You do not want to go with a medication that has no human exposures, so be very careful with medications with a B category. Don't assume they're safer than medications with a C category where animal studies show risk, but there are no control studies in humans or basically these categories are just a mess, which is why, as you might see, they're the old use in pregnancy ratings.

The only categories for from this list that you can trust are:

A: Controlled studies in women show no risk or

X: Risk outweighs any benefit

The B, C, and D categories are squishy, and you can't really base your choice of medications on those categories. You want to be basing your choice of medications on human exposures and on the newer categories.

New FDA Use-in-Pregnancy categories
Since June 2015, the FDA now has no more letter grades. Instead, they're narrative descriptions of risk. Unfortunately, these new categories only apply to medications approved after June 2015. Most of the psychiatric medications we use were approved before that.

Key point
The FDA does not require manufacturers to comply with the new system if the medications were approved before 2001, which is the case for many of the medications psychiatrists use.

You'll still encounter the B category and those older FDA pregnancy ratings. Just be careful how you interpret them.

Some guidelines
If prescribing medications for a pregnant woman, you want to document that:

- symptoms are improving with the medication
- the patient has capacity to consent to treatment
- you've reviewed baseline rate of birth defects (2-4%)

You want to document that symptoms are improving with the treatment. If not, why are you using it for such a vulnerable population? The patient should have capacity to consent to treatment. Make sure that she's not so ill, she doesn't know what she's consenting to. And very importantly, that you've reviewed the baseline rate of birth defects. Nature's not perfect; 2-4% of babies are born with birth defects for reasons we just don't know.

As I already said, don't choose medications solely on the basis of FDA Use-in-Pregnancy ratings. Go with human exposures. Emphasize how little is known about developmental outcome. As much as our data is growing on birth defects, we still don't know much about how that child is going to look at age five or six. It's important to warn patients that we don't have a of data on long-term developmental outcomes.

Maximize nonpharmacologic options prior to treating with psychiatric medications. Make sure patients are reducing stress in their lives. Part of the reason they might be experiencing, depression, for example, might be conflict in their marriage, or other stressors, which may require counseling. Make sure you're maximizing nonpharmacologic options as much as possible.

In cases of mild illnesses and where there are good protective features, like a strong support network and a history of responding well to treatment, careful discontinuation of medications before pregnancy may be feasible. I've been able to do this with some of my more stable patients, keeping in mind that we follow them very closely and resume the medications immediately on delivery or even in the last few days of pregnancy.

Alternatively, medications can be discontinued in the first trimester once you find out your patient is pregnant, so you keep her on the medication for as long as possible. Once she conceives, you can discontinue the medications at that point. Remember, you never want to stop medications abruptly. You want to taper over no quicker than two weeks, or you continue medications, but you switch to medications with good safety profiles.

ECT and pregnancy

I want to say something about ECT. It appears safe, rapid, and effective for patients with BD. The main complications are preterm labor and transient fetal arrhythmias, but these seem very rare. In a study of 33 pregnant patients, complete response to treatment was found in 84% of patients with major depression; 92% with BD; and 50% with schizophrenia. It has the advantage that there's very minimal exposure to the fetus of any medications, and it gets patients to turn around the quickest when compared to medications.

"Postpartum psychosis"

Now I'm going to switch gears and talk about postpartum psychosis. It's not described as a separate disease in DSM-5. It refers to:

1. mood disorder with psychotic features,

2. psychotic disorder not otherwise specified, or

3. brief psychotic disorder

For all three of these disorders, you would add the specifier "with postpartum onset," meaning within four weeks after delivery. But we just refer to any psychotic illness in the postpartum as postpartum psychosis, even though it's not an official illness in DSM-5. But for whatever reason, that's how it's been referred to in the psychiatric literature for decades, even though it's not an official diagnosis.

What are predictors of postpartum psychosis? These include an earlier onset of BD; multiple recurrences per year; a recent relapse of BD, especially if it occurred during pregnancy; and sleep disruption. In fact, this is one thing where we can intervene if a patient is wanting, for example, to breastfeed around the clock. I recommend against that because that could be so disruptive to sleep.

If a woman wants to breastfeed, that's great, but it's ideal if she has someone helping her at night so she at least gets some sleep and isn't waking up every two to three hours to breastfeed. She can pump and collect the milk and have a partner help with the feeding of the baby. It's very important to make sure patients are getting enough rest because that's such a simple way to help minimize relapses in the postpartum. Symptoms typically

develop very quickly. The vast majority of cases happen in the first four weeks after delivery. Women with BD at are at particularly high risk where about a third of them will have a postpartum.

As I just mentioned, what's the role of sleep deprivation? It does seem to play a big role. In fact, even fathers with BD seem to be at risk of relapse during this time if they're also waking up and not getting a good night's sleep. And a concern about postpartum psychosis is the delusions often involve the baby, that the baby is dead or that the baby is evil.

I had a patient with BD who gave birth to a healthy infant girl. Three or four days postpartum, she stopped taking care of her insisting the baby had died. This was a healthy baby girl, and this was an example of a delusion of a woman with BD with relapse in the postpartum. Delusions like that are not uncommon.

Postpartum psychosis: Prophylaxis

What about these women? If you have a woman with a history of postpartum psychosis or a history of BD, if they are not on medications during pregnancy, should they be prophylaxed before they deliver or immediately upon delivery? Yes, indeed. They should begin prophylactic treatment. That's absolutely essential.

This is a study that looked at women who initiated prophylactic treatment immediately upon delivery. None relapsed. In contrast, the relapse rate was 44% among women who declined postpartum prophylaxis. What about using lamotrigine for prophylaxis?

Here's a study that looked at women who had taken lamotrigine versus lithium during pregnancy. There was no significant difference in the rate of psychiatric hospitalizations between women who used lamotrigine versus lithium, although I'll say lithium seemed like the rate might have been a little higher, but still there was no significant difference.

Lamotrigine gives us an alternative treatment option for BD during pregnancy, as I mentioned earlier, and helps prevent postpartum. So it gives us an option besides lithium, since we might be a bit worried about using lithium in pregnancy given cardiovascular risks.

Mood stabilizers during breastfeeding

I want to switch gears and talk about breastfeeding. What are the risks of using psychotropic agents during breastfeeding? Some clinicians with experience of using lithium in breastfeeding might say lithium is okay to use during breastfeeding. I myself am a bit hesitant. Lithium levels can get quite high in a breastfeeding baby.

As all of you know, babies can get dehydrated very quickly. A bout of diarrhea or they're fussing and not eating well that day, and they can easily get dehydrated. If they're exposed to lithium through breastfeeding, their serum lithium levels can reach significant levels if the mother is on lithium, so I don't like having a baby exposed to lithium through breast milk.

Carbamazepine and valproate, as much as we worry about them in pregnancy, are actually okay in breastfeeding. They're highly protein bound, and they don't traverse into the breast milk readily. Lamotrigine also appears okay in breastfeeding.

Antipsychotic meds and breastfeeding
Antipsychotics also seem okay, although the total number of reported exposures is low, but there have been no adverse outcomes.

Pharmacokinetics

When I'm unsure about a medication and breastfeeding, I like to look at pharmacokinetics. In fact, I used to do research on breastfeeding and psychotropic medications, and what I found was that predictors of infant exposure to psychiatric medications and breast milk were these two pharmacokinetic factors: (1) how protein bound is the medication and (2) what's the half-life?

The ideal medication is something that's highly protein bound because less will traverse through the breast milk to the baby, and something with a short half-life, because it won't accumulate as much in the breast milk.

Ziprasidone would be ideal. Risperidone looks decent. Quetiapine is OK. Aripiprazole has the disadvantage of a very long half-life. Olanzapine is OK, but the half-life is also somewhat long; at least it's highly protein bound. In the absence of human data, which is often the case with antipsychotic medications and breastfeeding, you can go with pharmacokinetic parameters, to help you predict the exposure to the infant.

Summary: Management of BD in pregnancy
To summarize, the management of BD in pregnancy is complex. There are no risk-free options. You're always weighing the risk of medication exposure with the risk of relapse of BD and pregnancy in the postpartum. There's great individual variability. Some women can go years without a relapse and might be okay to have them be followed closely off medications during pregnancy and the postpartum, while other women have a lot of relapses, as soon as they stop medications and you have to keep them on medications during the pregnancy and postpartum period.

Even women who are on medications that are well-treated might still relapse because the perinatal period is just simply a high-risk period for women who are at risk of having relapses to mood disorders. You want to manage on a case-by-case basis. Begin treatment, at least six months prior to efforts of conception. Begin your management at that point to choose the safest medication options. Any medication changes should be gradual, as abrupt changes can themselves increase the risk of relapse.

Recommendations
You want to avoid valproate and carbamazepine in pregnancy given the risks of neural tube defects. First-line choices for pregnant women are lamotrigine and quetiapine. If using lithium, monitor blood levels at least monthly, and remember, the postpartum is a very high-risk time for relapse. About one in three patients will relapse if untreated, so it’s best to treat prophylactically.

Thank you for your attention and I hope you learned something from this presentation.

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