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Advances in Postpartum Depression: What You Need to Know

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Advances in Postpartum Depression: What You Need to Know” was presented during Omnia Education’s Women’s Health 2021: Beyond the Annual Visit.

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Dr. Clayton:
Hi, I'm Dr. Anita Clayton. I'll be presenting today on Advances in Postpartum Depression: What You Need to Know. These are my financial disclosures. I mostly have relationships with pharmaceutical companies that are developing treatments for major depressive disorder, and for postpartum depression, and for sexual dysfunction.

The learning objectives today are to be able to describe validated tools for identifying patients with postpartum depression, or PPD, outline the current evidence-based strategies for optimal treatment of mild, moderate, and severe PPD, discuss the efficacy and safety findings from clinical trials of approved and emerging therapies for PPD. So let's get started.

I think it's useful to think about a unified theory of depression and how it occurs. And Dean and colleagues have developed this, and I've put a modified version on the slide. The etiology really seems to stem from genetic and epigenetic susceptibility, and then environmental triggers. So we're talking really about nature and nurture. That contributes to pathophysiology that occurs in a number of areas. So we already know about monoamines, like serotonin, norepinephrine, and dopamine, with their function being diminished. Also, though, GABA can be diminished, which is a primary inhibitory neurotransmitter, and glutamate can be increased, which is a primary excitatory neurotransmitter. Neuroactive steroids are also involved. And inflammatory mechanisms contribute to a hyperactive HPA axis. All of these combined, or even just one, or a couple of them in a given individual will act to reduce neuroplasticity and cause neural network dysfunction. And as a result, we'll see a clinical phenotype of MDD and PPD.

Now perinatal depression is common. So I want to talk about depression during pregnancy first, because many women who have a postpartum depression are already experiencing depression during pregnancy. Overall, the highest rates of major depression occur in reproductive age women, and 10 to 16% of women who are pregnant have MDD. That rate really increases after the first trimester, as we're seeing huge shifts in hormones. And it's turns out to be twice the rate we see in the general population by, month four. It's often associated with a prior history of depression, specifically other reproductive-related mood disorders like premenstrual dysphoric disorder, or depression during a prior pregnancy. And when the antidepressant medication is discontinued, because they're planning for or because they've found that they are pregnant, about 70% of women will relapse with MDD during the pregnancy. And that relapse rate is significantly higher for women with severe or recurrent depressive episodes.

Women with a prior history of major depressive disorder, will often develop depression during pregnancy or in the postpartum period. So this increased risk is greatest among women who had a previous history of a postpartum depression. And that rate is at least 50%, and some other studies have suggested as high as 90%. With regards to postpartum depression, up to 80% of new mothers experience what we call the baby blues. This is a period lasting one to two weeks of mild worry, unhappiness, emotional lability, crying, and fatigue.

This is not a woman who is experiencing depressive symptoms or a sense of depressed mood, and she'll often be un - unaware of what has caused her to cry, or why she is crying at any given moment. However, these symptoms resolve without any intervention in the vast majority of women. Some women, however, go on to develop a postpartum depression, which is a major depressive episode, beginning within four weeks of childbirth. Although we sometimes see later onset in women who are breastfeeding, after they wean their baby. This onset of postpartum depression early after delivery appears to be related to a rapid drop from extremely high levels of estrogen and progesterone during pregnancy to prepregnancy levels, and this occurs in the first three days after delivery. So many women may not be able to adapt to those rapid changes, and this triggers a depressive episode. Also, some women are particularly sensitive to hormonal mood changes that are normal. So these are normal changes after delivery, but they may also be sensitive to things like the change in hormones that occur that contribute to premenstrual dysphoric disorder or the changes in hormones that are happening around the time of the peri premenopause. So postpartum depression is seen in 10 to 15% of women.

It's important for us to screen, and the easiest way to do that is to use the Edinburgh Postnatal Depression Rating Scale. We do screen during pregnancy and use this same scale. So, it's called postnatal, but it's really perinatal.

This was a study done in over 10,000 women who were evaluated within four to six weeks postpartum, and they filled out the EPDS. Fourteen percent were screened positive with a score of greater than or equal to 10. And that's consistent with what I just told you about postpartum depression being seen in 10 to 15% of individuals. The more concerning part is that only 40% of those episodes began postpartum. Whereas a third began during pregnancy, and over a quarter had been ongoing since before the pregnancy. Seventy percent had major depressive disorder, two thirds had comorbid anxiety disorders, and almost a quarter had bipolar disorder. And this puts women at increased risk of postpartum psychosis and potentially with adverse reactions, in terms of developing many - manic episodes, if we utilize routine antidepressant therapy. So it's important to eliminate that as a possibility in women who were experiencing a depressive episode postpartum.

Almost 20% had self-harm ideation to which is highly concerning. Drug deaths, overdose, and suicide are major contributors to maternal death in the 12 months after delivery. So it's important for us to identify this early on and ensure safety.

This is the Edinburgh Postnatal Depression Rating Scale. You can see it has 10 items. Item 10 is critical for us to review, because that is the one that evaluates for self-harm. Some of these items are reverse scored; otherwise, items are scored from 0 to 3, and a score of 10 or more suggests depression. Scores of 7 to 13 indicate mild depression, 14 to 19 indicate moderate depression, and 19 to 30 suggests severe depression. We should do a further evaluation to determine that they do specifically have major depressive episode in the postpartum period and do not have bipolar illness.

Now let's talk about the mechanism of action of potential treatment options. Standard oral antidepressants act on neurotransmitter, serotonin, dopamine, norepinephrine and primarily as reuptake inhibitors. So that's why we see SSRIs, SNRIs, et cetera. And these boosts neurotransmitter activity and/or make the activity last longer at the synapse, which therefore improves neurotransmission.

Very different mechanism of action occurs with neuroactive steroids. These have been evaluated in PPD because they bind to gamma amino butyric acid type A receptors, so GABA A receptors, and act as positive allosteric modulators. There are two binding sites, synaptic binding sites, where benzodiazepines bind and this is on the gamma subunit. And this leads to rapid but brief or phasing effects. And then extrasynaptic receptors with the binding site on the Delta subunit for the positive allosteric modulators and like the endogenous one allopregnanolone, which is a progesterone metabolite, and brexanolone and zuranolone, which are potential medications that – that also bind to that site. And this leads to rapid but also sustained or tonic effects. These effects open the chloride ion channel through the membrane and keep it open to enhance GABA inhibition of hyperactive neurotransmitter systems and, therefore, restore neuroendocrine network functioning and relieve symptoms of PPD.

A couple of pearls for treatment in pregnancy. As I mentioned, use that EPDS for - for evaluation and screening during the pregnancy and beyond. So if you've been monitoring during pregnancy, and then you go ahead and monitor postpartum and after an intervention is made, you can evaluate for treatment responses and outcomes. If a woman stopped her antidepressant due to pregnancy, and depression recurs, I suggest restarting the previously effective medication. Because past history of response really guides our treatment. We don't have time to mess around and find something else that works. We should utilize something we know has been effective, even if there's somewhat less information about it than, um, the recommended, treatments during pregnancy. Those are because we have a lot of data about them.

If a woman has never been treated before, then we have the most data available for fluoxetine during pregnancy unless she plans to breastfeed, and then we use sertraline, because it has low levels of the antidepressant in breast milk.

Don't under treat during pregnancy. A lot of times people keep the dose low because they're worried about any risks associated with increasing the dose. But the risks of medication exposure are not dose related. Maximize the use of one medication And increase the

dose as pregnancy progresses if symptoms are increasing, because we're seeing increased volume of distribution and increased drug metabolism in women as they progress in their pregnancy. Avoid exposure to both drug and continued depression. So don't start an anti-depressant, keeping the dose low, and then have them continue to be depressed. That gives us the worst fetal outcomes. And don't reduce or stop the antidepressant in the third trimester. This is a recipe for postpartum depression.

In the postpartum, if someone's had a prior episode of postpartum depression, plan in advance. If they're not depressed during the pregnancy, and you haven't restarted that medication, and they want to avoid any symptoms of PPD, which most of my patients want, we start the antidepressant right at delivery. So literally, I tell the mom, ‘When that baby pops out, you're gonna pop in that pill and we'll get started.” And we've got a few days to a couple of weeks to get ahead of onset.

If the first episode of postpartum depression is mild to moderate per the EPDS, start an oral antidepressant or initiate psychotherapy, like cognitive behavioral therapy, or CBT, or interpersonal therapy. Utilize SSRIs, SNRIs, Bupropion or mirtazapine, if you're utilizing an antidepressant. And titrate to a therapeutic dose, and continue that dose for six to eight weeks to see the full effect before you consider changing or augmenting treatment. If they were previously treated for any kind of major depressive episode, use the medication that was effective and don't withhold treatment due to breastfeeding because exposure is much lower in breast milk than in utero, and self-tapering will occur with weaning.

If the postpartum depression is moderate to severe, especially if a rapid response is desirable, and when is that not true, treat with brexanolone. Brexanolone had, has gotten approval by the Food and Drug Administration. So let me tell you a little bit about the brexanolone Phase 3 trials. Brexanolone is a neuroactive steroid GABA A receptor agonist positive allosteric modulator that is administered in 60-hour inpatient I.V. infusions. Women were enrolled who were less than six months postpartum, had a postpartum depression, and were willing to temporarily stop breastfeeding during the course of the treatment. There were two studies, the primary efficacy measuring both was the change in Ham-D 17 total score at 60 hours.

In Study 1, patients were more severe with an inclusion Ham-D 17 score of greater than or equal to 26; 138 subjects were enrolled, and they were randomized to either have a titration up to 60 micrograms per kilogram per hour of brexanolone, or up to 90 micrograms per kilogram per hour of brexanolone or placebo. There was a significant and rapid response with both doses, um, a decline of 19.5 points on the Ham-D 17 with 60 micrograms, and a decline of 17.7, points on the total Ham-D score with 90 micrograms. And these were significant versus placebo, which had a – a Ham-D score drop of 14. There was one serious adverse event of suicidal ideation and overdose in one patient.

Study 2 was more moderate to severe postpartum depression with Ham-D 17 scores of 20 to 25 at baseline; 108 subjects were included, and only 60 micrograms per kilogram per hour brexanolone was studied versus placebo. Again, significant drop at 60 hours in , the dose with brexanolone, this was 14.6. And this was significant versus placebo where the drop was 12.1. There was a serious adverse event of altered mental status and syncope in one patient. There was really no difference in adverse events from placebo. The most common were headache, dizziness, and somnolence.

It might be easier to see the - the real difference between placebo and brexanolone in this study, which was a Phase 2 trial.

This is really evident in the graph, that there's a significant drop in Ham-D 17 total scores with brexanolone that occurs by 24 hours. And then that effect is maintained through the end of the infusion at 60 hours and continued out for 7 days and 30 days. About 70% of women achieved remission with brexanolone versus only 9% with placebo. And the, Ham-D effect size is 1.2, which is really significant. Similar results were seen with other measures like the MADRS and the CGI.

Brexanolone was subsequently FDA approved for PPD, and they approved both the 60 and the 90-microgram dose. They acknowledged common adverse effects like somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, sedation, and nausea, and noted the rapid response and sustained response with brexanolone.

The Advisory Committee left the decision of whether to utilize 60 or 90-microgram dosing up to the FDA. However, they did recommend a REMS, and that brexanolone should be administered in medically supervised settings, with a pulse oximeter being utilized through the 60-hour infusion and for 12 hours afterwards. A healthcare provider should be available to intervene for sedation or loss of consciousness. An assessment needed to be made for excessive sedation every two hours during any planned non-sleep periods. Additionally, if their baby was present with them, an additional caregiver needed to be there in case mom is too sedated with the infusion.

It is also suggested that pausing breastfeeding during the infusion and for 36 hours after completion of the infusion, be done. A woman could pump and dump during that time period, but not to necessarily provide that breast milk to her baby.

Now, zuranolone is currently under investigation for treatment of postpartum depression and major depressive disorder. The ROBIN

study was a Phase 3 trial looking at zuranolone in PPD. It is an oral neuroactive steroid GABA A receptor agonist positive allosteric modulator, much like brexanolone. One hundred and fifty-three women with severe PPD were randomized to placebo or zuranolone 30 milligrams, which was taken daily for 14 days in the evening. About 20% of the women were taking an oral anti-depressant medication before enrollment and continuing through the study. At days 3 and 15, which is the primary endpoint, and day 45, there were significant differences in the reduction in Ham-D 17 total scores for zuranolone versus placebo. And differences in both response and remission rates were also significant, and favored zuranolone.

It was also well tolerated with similar rates of adverse events reported for zuranolone at 60% versus placebo at 52%. The most common adverse events are somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, sedation, and nausea. It does not cause severe sedation or loss of consciousness. And so this is dosed at home.

You can see the same kind of rapid drop in Ham-D 17 total score, as was seen with brexanolone, only it's over a somewhat extended period because of the 14-day treatment. Significant drops were seen at day 3, day 8, and the primary endpoint at day 15, as well as days 21 and 45, indicating sustained effect out for six weeks. The day 15, which was the primary endpoint drop in Ham-D score was 17.8 versus 13.6 with placebo. The other P values varied between 0.03 and 0.003. Zuranolone, as I mentioned, was well tolerated, and discontinuation rates were low.

So in conclusion, some women are sensitive to normal hormonal changes that may represent a period of higher vulnerability for depressive episodes for these women. We need to monitor them for mood changes and depressive symptoms during these higher risk periods.

Medications acting on serotonin, GABA, dopamine, and monoamine oxidase have a bidirectional relationship with sex steroids and appear more effective for hormonally mediated mood disorders. For mild to moderate PPD, standard of care oral antidepressants are effective and well tolerated.

For moderate to severe PPD, the neuroactive steroid GABA A receptor agonist positive allosteric modulators, brexanolone and zuranolone, have both phasic and tonic effects that enhance inhibition of a hyperactive HPA axis and rapidly relieve symptoms of PPD. Other interventions such as lifestyle modifications, dietary changes, stress management, psychotherapy, and/or phototherapy, combined with pharmacotherapy may provide the best outcomes. Thank you.

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