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Improving the Detection and Prevention of PPD: The Potential Role of Biomarkers

Ashley Baker:
This is *Advances in Women's Health* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and joining me to discuss her study on predictive biomarkers in postpartum depression, or PPD for short, is Dr. Lauren Osborne. She's an Associate Professor of Obstetrics and Gynecology as well as an Associate Professor of Psychiatry at Weill Cornell Medicine, NewYork-Presbyterian Hospital. Dr. Osborne, welcome to the program.

Dr. Osborne:
Thank you so much. I'm very glad to be here.

Ashley Baker:
To start us off, Dr. Osborne, can you provide some background on your study and why you decided to focus on biomarkers in PPD?

Dr. Osborne:
Absolutely. So one of the things that we do very badly in our society is identify and treat women with postpartum depression. Only about 3 percent of women with postpartum depression actually get treated all the way to remission, and that's because we do a really bad job all the way down the cascade: identifying, diagnosing, starting treatment, and getting the appropriate treatment. I've long thought, and my research group has worked on the idea, that if we had a better way of identifying who is going to be at risk, we might do a better job of taking the scarce resources that we have and applying them to those patients who are most at risk. And because I'm a biological researcher, of course I think about biological ways to determine who's at risk, so I've worked on several different ideas over the last few years that are potential biomarkers for postpartum depression, and this new paper is one of those.

Ashley Baker:
So with that context in mind, what methods did you use for your study, and how did they help identify the link between neuroactive steroid levels and the risk of PPD?

Dr. Osborne:
Yeah. So we've known for a long time that neuroactive steroids play some kind of role in the pathophysiology of postpartum depression. There's been about 20 years of basic science research on the neuroactive steroids, and there was a drug developed a few years ago that was the first drug ever approved by the FDA specifically for postpartum depression that works on that mechanism. But we haven't known exactly what the defect is in neuroactive steroid synthesis or metabolism that is leading to the symptoms of postpartum depression. Many studies have looked at one or two neuroactive steroids, and we decided to look at the whole neuroactive steroid pathway that comes from progesterone. We were using metabolites of progesterone that are active in the brain and looking at progesterone itself and then all the molecules that are downstream of progesterone, and we wanted to look not just at what one or another of these does to the brain, but the interaction of the whole system and the ratios of those that are positive effectors on the receptor in the brain and those that are negative effectors and whether that might be involved in people's susceptibility to postpartum depression.

Ashley Baker:
And turning to the results, what were the key findings?

Dr. Osborne:
So what we found was that in the third trimester, when we looked at women who were euthymic in pregnancy—meaning they were not

depressed in pregnancy but they went on to develop postpartum depression, and we compared those to women who were also not depressed in pregnancy but did not develop postpartum depression—we found that the women who did develop postpartum depression had higher levels of progesterone, and they also had a higher ratio of one of the negative metabolites of progesterone to one of the positive metabolites of progesterone. So what that means essentially is that there's something broken in that progesterone metabolic pathway. Some women may be getting stuck at progesterone and not metabolizing all the way through to the end streams of the products, which are the things that are active in the brain; for some other women, there's an imbalance between those molecules that have a negative effect on the GABA receptor, which is the receptor that makes people feel calm and good, so there's an imbalance between those that have a negative effect on that receptor and those that have a positive effect on that receptor. So we don't know at this point whether it's the enzymes that control those pathways or whether it's a genetic defect in one or the other of these molecules, but we've identified that it's something in this pathway that's giving people that vulnerability to develop postpartum depression.

One of the key things to think about also is how these molecules interact with the receptor in the brain. So the levels of these molecules actually affect the way the receptor configures itself during pregnancy. It undergoes a major change in pregnancy and then a change back in postpartum, and if we don't have the right levels of the right neuroactive steroids, that affects the way the receptor changed, so you have to look at the two things together.

Ashley Baker:
For those just tuning in, you're listening to *Advances in Women's Health* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and I'm speaking with Dr. Lauren Osborne about findings from her research on how predictive biomarkers may improve the early identification and prevention of postpartum depression, also known as PPD.

So, Dr. Osborne, let's shift gears now and talk about the implications of these results. How can measuring neuroactive steroid levels during pregnancy help identify women at risk for PPD earlier, and how might this change current clinical practices?

Dr. Osborne:
So the current way that we identify people at risk for PPD is very imprecise. The American College of Obstetricians and Gynecologists recommends that we screen women for symptoms at three time points: at the first prenatal visit, sometime during the third trimester, and then again at six weeks postpartum. And that method works well if two things are in your favor: one, if the people already have symptoms to be detected on a screening scale, and two, if you can incorporate that screening into your practice, which is actually much more logistically difficult than you would think. So we don't adequately do that with women. In addition, those methods rely on people to have symptoms at that time. It doesn't tell us who's going to be at risk of developing future symptoms. So if we had a blood test that could predict in pregnancy who was at risk of developing symptoms in the future, that would help us catch those women who aren't going to be caught by a screening test because they aren't sick yet and then it would help us to, as I said, direct our scarce resources toward those women. We could get them into some kind of preventative treatment. That might be psychotherapy or it might be medications depending on the particular person and her history. It might be thinking of a new preventive use of that new medication that is a neuroactive steroid. I think there are lots of options if only we knew how to identify those people before they became ill.

Ashley Baker:
And what impact could these findings have on postpartum care for new mothers, particularly in terms of prevention or early intervention?

Dr. Osborne:
I think it's prevention that's key. So one of the things that psychiatry struggles with in general is having other clinicians take us seriously as a medical discipline. They tend to think psychiatry is something different and separate and that our illnesses aren't real illnesses, and one of the reasons for that is that we can't show any blood tests; we can't show any objective proof that somebody has a particular disorder. If we have a blood test, I think that will go a long way toward reassuring both patients and other clinicians that these are biological disorders that may have biological treatment, so I think there will be much more of a buy-in to the idea that we could use a treatment to prevent the onset of postpartum depression. So that's one way, but also, it will just help us identify those women and get them into the good treatments that exist.

We have great treatments for postpartum depression. There's a number of psychotherapy approaches that have been very effective. Cognitive behavioral therapy, the Rose intervention, and interpersonal therapy all have good evidence for postpartum depression. In addition, the SSRIs, which we use for depression at times outside the perinatal period, are likely effective in this period. I say likely because there aren't a lot of studies, but they're in clinical use, and people tend to respond well to them. And then there are the new drugs that are specifically for postpartum depression. So we have good treatments there. We just aren't good at getting the right people to those treatments early enough and early enough that we can prevent the onset, and a blood test like this would help us to direct those people to the right place.

Ashley Baker:
As we come to the end of our program, Dr. Osborne, let's look ahead for a moment. What are the next steps in your research, and what do you hope to uncover as you continue studying postpartum depression?

Dr. Osborne:
Yeah. There are many next steps in this research. We're relatively early days yet. We've identified this defect, as I mentioned, in that metabolic pathway, but now we need to figure out exactly what the defect is. Is it a defect in the enzymes? Is it a defect in the way the altered levels of these neurosteroids affect the receptor itself or the configuration of this receptor that changes during pregnancy? And so we have a new study coming up that we're just embarking on. We are about to get a new grant to study this particular pathway with exactly those things: the subunits of the receptor and the enzymes that control the expression of these metabolites. So we'll be carrying that study out; it will be a four-year process to enroll a new set of pregnant participants and really try to figure out those additional steps so that we can pinpoint with accuracy exactly where the defect is. And then after that, there would be a long process, if we're successful, of turning this into something that's clinically useful. This isn't the only thing that we're pursuing. We also have a potential biomarker in extracellular vesicles that are tied to immune cells in the body. That's also a very promising target, and we're working on that.

So my goal really is to find biological evidence that shows what's going on in the biology of women who develop postpartum depression. People can develop postpartum depression at any time in the first postpartum year, and not all of it's biologically linked. You may develop depression later in that postpartum year because you're having struggles with your partner, you're not getting enough sleep, or you've had changes at your job, but in people who develop it really close to childbirth, there is that biological link; and if we can figure that out and develop new treatments, not only does that help women with postpartum depression, but it also gives us a clue into how we might develop biomarkers for depression that are not in the perinatal period. We have such an obvious trigger for postpartum depression that it's kind of low-hanging fruit to go after that.

Ashley Baker:
With those forward-looking insights in mind, I want to thank my guest, Dr. Lauren Osborne, for joining me to discuss her study on the potential impact of neuroactive steroid levels on predicting and managing postpartum depression. Dr. Osborne, it was great having you on the program.

Dr. Osborne:
Thank you so much for having me. It was a lot of fun, and I hope your listeners will be as jazzed up about this work as I am.

Ashley Baker:
For ReachMD, I'm psychiatric nurse practitioner Ashley Baker. To access this and other episodes in our series, visit *Advances in Women's Health* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.