[MUSIC PLAYING]

ANGELA O'NEAL: It is my distinct honor to introduce Dr. Page Pennell. Dr. Pennell is now your new chief of neurology at UPMC. She's a world expert in women's issues in epilepsy. And on a personal note, she's a wonderful, wonderful role model and mentor. Dr. Page Pennell.

PAGE PENNELL: Thank you, Angela. And thank you everyone for joining us in person and many of you who are here remotely. I just have to take a quick minute to really acknowledge the course directors. Woman neurology wasn't even a thing that anyone spoke about, even though we know how important women's health is across many other areas, and now it's getting acknowledged in neurology.

And so I had the pleasure of working with Angela O'Neal and seeing her build up the program at Brigham. And it was hard for me to leave Brigham for many reasons, including that incredible program. But it was OK, because Janet Waters was here. And being able to carry on, both of them, the work that actually that Adam Klein started, and now Amy Hessler joins this group. So huge acknowledgment to the three of you and what you're doing to really change the field. So it's a pleasure to be here. Here are my disclosures.

So one of the things I like to speak about when talking to providers is, as we think about management of women with epilepsy during pregnancy, to also remember how many women actually are given these same medications for other things. We heard about, of course, migraine. Also other pain disorders, bipolar disorders, and other psychiatric indications. So about three times as many women are actually given medications which we call antiepileptic drugs-- or our new term is anti-seizure medications-- and are given during the reproductive years. And one study shows that over 2% of women were exposed or had exposure to these medications during pregnancy.

So I think still the same principles-- how do we manage the underlying disorder-- just as you heard about for headaches, migraine-- and keep it relatively controlled, balancing the fetal risk. So for these medications we do have a lot of concrete data now compared to a while ago. The first things that came out were the risk for major congenital malformations. But now we have much more information about which medications have the higher risk.

And then work by Kim Meador leading the way almost 20 years ago-- I guess 20 years ago now-- looking at the neurodevelopmental effects. So we have to think about exposure through the entire gestational period, and what are the consequences of the medications crossing into the fetal compartments, and especially crossing into the fetal brain. And now we also have this new information that not only do we need to think about the type of medication we prescribe, but the amount of medication we prescribe. So we need to think about keeping the fetal exposure low but maintaining seizure control. So it gets a little tricky how to balance all of that together.

Next slides are courtesy of Torbjorn Tomson-- or this slide-- so I just want to give him the recognition. He is the head of EURAP, which is a pregnancy registry around the world, 42 countries, several continents. And he also put together this graph that also showed data from the North American AED pregnancy registry which, everyone, please remember to refer your patients to. Call the North American AED pregnancy registry. It's only like a 15-minute call in the beginning, 5-minute call third trimester, and 5-minute call after delivery.

And then the UK and Ireland pregnancy register-- so on the left, you can see the y-axis is the rate of malformations. And I always start the counseling with the patient and her family with reminding them that major malformations-- or birth defects often refer to them-- occur in the general population at a rate of around 1.5 to 3%. And our goal is try to get her risk as close to the general population or to the general population.

So it's really important to remind them. And then if something happens that also they feel like, well, it's not necessarily only happened to my baby because I took medication. So here are the rates of malformations. And you can see that we have consistent signals across registries for lamotrigine and levetiracetam for low malformation rates with tight confidence intervals. So that's what we love to see.

Only recently, actually, we got this information that oxcarbazepine rates are really actually quite low as well. We're not quite there on confidence intervals, but still there to now be able to say, actually, the rates are lower than carbamazepine. So that's, to me, a relatively new clear evidence to keep in mind. Then you can see topiramate, carb, phenytoin, phenobarbital, and, as we all know, valproate, with the highest rates of malformations and which actually increase with even higher doses.

The other principle I mentioned early on is that even if we choose a quote, "safe" medication, we have to think about how much exposure there is. This is from EURAP, and this was the dose at the time of conception. So it's a little bit kind of confusing. Might feel like you're getting mixed messages. But this is the information they had. So at the time of conception, even for all the medications they were able to have enough power to look at, there was a slightly increased risk with higher doses.

So if I have a woman, for instance, who I can have her seizures controlled at under 325 milligrams per day of lamotrigine, then I try to get her to that lower dose prior to conception. Now I'm just going to segue for a second. So there's one really common time that you would want to consider decreasing the dose of lamotrigine going into a planned pregnancy. And I guess I can't ask the audience, but I know all of these ladies know, and many of you.

So if they're on a birth control pill, equivalent would be 600 milligrams per day on a birth control pill. But if you take the birth control pill off because planning pregnancy, then you should be lowering their dose. I do it stepwise to about 300 milligrams per day. So that is a great opportunity to lower the risk going into a pregnancy that you do not want to miss.

And likewise for all the medicines they looked at, the rates were higher. With higher doses of carb, phenobarbital-- even broke down into three levels of risk-- and then valproate, as I mentioned, and over 1,450 milligrams per day, which isn't an outrageously high dose, it's a common dose, rates go up around 25% for malformations. So moving on to what we now also think about, is the medication exposure throughout pregnancy, and with Kim Meador leading the NEAD study, able to show that valproate children had lower IQ after exposure to valproate in utero.

One thing also that changes my practice is that if the mother was taking folate prior to conception and continued it, her children actually did better in IQ. So I've always preached, starting at menarche, you should just take folic acid every day, because 50% of our pregnancies are unplanned. But now they'll say, why, and you kind of go through everything. But now that I can say, actually, your babies will be smarter if you have an unplanned pregnancy, they're more willing to take the folate. So it's interesting sort of what resonates with our patients.

The other thing that we know is not only IQ but actually the risk of autism is quite a bit higher with valproate. So here's adjusted hazard ratio at 1. And you can see how high the rate is for autism diagnosis or autism spectrum disorder. So really based upon these neurodevelopmental effects, all these additional restrictions came out for prescribing valproate with the FDA. But in Europe it even got more extreme, where you had to have a special license to use it. And I believe in the FDA here, it even changed to category X for migraine, I think. And for bipolar or epilepsy, it says it can only be given if all other treatments have failed.

Also there is a controversy about, well, the malformation rates-- if you go back a few slides, weren't that large if the valproate dose was low. And of course, some people have to have valproate. It's the only thing that will control their seizures and some of the primary generalized epilepsies. But for the autism, the rates of autism were the same if they were on low dose versus high dose, so something to keep in mind.

This slide is important but also in honor of the late Dr. Autumn Klein. This was a study she started when I went to Boston and started working with her at Brigham. And she got the funding and led this study to look into the North American pregnancy registry-- what are the rates of small for gestational age. So her work with Dr. Tom McElrath-- he's the obstetrician we work with and Angela continues to work with-- really taught me again, it's not just malformations but also small for gestational age, places that baby at risk later for many, many other long-term health issues-- cardiovascular risk, obesity. There's actually some developmental effects or association.

So they really taught me to think about this as well. And to be honest, I was completely clueless until I met Autumn and she taught me about how important this is. So within the North American pregnancy registry, we were able to show that the rates of small for gestational age were particularly high for topiramate but also high for phenobarbital and zonisamide, and then a little bit for valproate, which we also saw in the NEAD cohort.

The red is a little confusing, but it's just, compared to lamotrigine, what is the adjusted risk ratio. So when you, in other words, because we always as practitioners, we think most of our women with epilepsy can't come off medication. So what can I do if I prescribe lamotrigine versus topiramate. So we like having that comparison. And that's what the red dots indicate, the risk ratio compared to lamotrigine. And the bars are the actual rates as small for gestational age.

In the North American registry they also saw a higher risk of prematurity for all medication groups 1.5 times higher. So I'm going to interweave in-- so after NEAD, we started the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs, the MONEAD study. And this is where Kim Meador invited me to join him as a PI because of my prior work and interest in how do we maintain seizure control.

And so we decided to take a new cohort and not only look at neurodevelopment but look at maternal outcomes with regard to seizures, obstetric complications, depression, and children outcomes with regard to neurodevelopment again, but also neonatal complications and the effects of breastfeeding. And this time we obtained blood work throughout the study and also looked everything in a model of how much level of exposure there is and pharmacokinetic changes. So NEAD was designed specifically to only look at four groups of women on monotherapy with either phenytoin, carbamazepine, lamotrigine or valproate, because that was the prescribing practice back then, and again, about 20 years ago.

But now, when we designed MONEAD, we said, let's just take all comers. We're not going to say, we're only going to look at certain medications. And so this is the prescribing pattern in MONEAD with lamotrigine, the most common monotherapy, but almost the same with levetiracetam monotherapy. This combination of lamotrigine and levetiracetam was quite common for a polytherapy. And a lot of those are an attempt to avoid valproate. Other polytherapy combinations-- carbamazepine, zonisamide, ox carb, topiramate, lacosamide-- four women on felbamate, who would have thought-- other monotherapy and then valproate. We only had four women on valproate out of 355 enrolled women.

So this pattern actually also is the same as what is coming out in the EURAP articles, which is that pregnancy registry around the world. So it's not to say in a developing country where they don't have access to the medications this would be the prescribing pattern, but at least in the developed countries with access, this tends to be what's favored for use during pregnancy now.

Also a call out to University of Pittsburgh-- was also an enrolling site and contributed to the study. So a paper we recently published were the two-year-old outcomes of the children and the bottom line is that there was no difference between healthy pregnant women's children. So in this study we also had two control groups and one was healthy pregnant women and comparing, there were no differences in the Bayley Scales of Development.

However, there is a little bit of an indication that higher medication levels in the third trimester were associated with slightly lower scores on-- this one was motor and adaptive domains. But now we're looking at the three-year-old, and it's an abstract form that it's affecting verbal. But it's still early, so don't want to hang our hats too much on that. But as we follow the children until age six, we will be looking to see if higher levels in the third trimester, or specific medications with higher levels, have some impact on the children's development. But overall, it's very good news. Encouraging.

So we talked about the risk of malformations and the risk of seizures. So how do we balance-- the risk of-- sorry-- for malformations and the risk for neurodevelopment. But how do we balance that against the risk of seizures? And our obstetric colleagues are particularly really wonderful and great about reminding us, you first treat the patient. We can't do everything and put the woman in a bubble and say, you know, she's just a gestational carrier.

So for some women, it's really an individual conversation. It's really interesting how varied it is. Some women will say, if they have, let's say, focal aware seizures with dystonia, dystonic posturing of the right arm-- I had one woman, like, I'm fine. Go ahead, take my dose down and we'll see prior to pregnancy. And they got more frequent, but they didn't progress to worse seizure types. And she wanted to continue that pattern during pregnancy. And then I have other women who are like, don't let me-- don't let me have a seizure. And of course, the type of seizure is a big difference. If you take away their ability to drive, if they have any impaired awareness, and obviously, convulsive seizures we want to avoid completely as much as possible.

So we can't do controlled studies for our talks all today. And so we have to just look at both prospective observational studies such as MONEAD, but also still pay attention a little bit to anecdotal reports. So there are reports of cases with generalized tonic-clonic convulsions resulting in miscarriages and stillbirths.

There is one study that showed if the woman had five or more convulsions during pregnancy, the child was at higher risk of developmental delay after adjusting for other factors such as medications. We do know convulsion causes maternal hypoxia and acidosis, and of course, that's going to affect the fetus. There is one nice case report from Texas a long time ago that was having monitoring-- fetal monitoring during a focal seizure that only lasted two minutes, but there were signs of fetal distress for 30 minutes.

So we still think about the effects of other seizure types as well. And the Taiwan birth registry, which had over 1,000 women with epilepsy compared to over 8,000 controls, with that kind of power did show that there was increased odds ratio for low birth weight, small for gestational age, and preterm delivery with all seizure types.

And I won't go into all the details, but the elevated maternal mortality is real. So there's almost a tenfold increase risk of dying during pregnancy with the diagnosis of epilepsy. Of course, the baseline rate is low but it's significant. And in the UK, where they were able to look at details, they were able to see that many of them were due to sudden and unexpected death in epilepsy.

So when we looked at prior studies, it was all over the place. 75% of women have seizure worsening. 9%. And of course it matters a lot. It matters about adherence. It matters what the practitioner is advising the women. But there are a few studies that show the benefit of therapeutic drug monitoring. It is important to have this basic principle even though it's, I know, very boring probably to most people. But just trying to put us in the same frame of mind-- clearances, how much dose do you need to give to maintain that person's concentration.

So you have a woman with a levetiracetam level-- you really should try to have it prior to any planned or unplanned pregnancy, so I get it in all our women at some point-- at which their seizures are at their best control. And if I wanted to maintain levetiracetam 15 micrograms per milliliter per day throughout pregnancy, then how do I need to change the dose during pregnancy?

And it really has nothing-- not nothing, but very little to do with weight gain. So we can't weight for weight gain. So this was old work but just showing that lamotrigine clearance increased. This was a single-site study at Emory where lamotrigine clearance increases on average two to three-fold. We looked at free levels, it was the same. So you don't need to monitor free lamotrigine.

More importantly, what we were able to show is if the level dropped to less than 65% of her pre-pregnancy level, then the risk of seizures went up. So this was a while ago in 2008 and it made it into the AAN guidelines, the last ones that came out in 2009. They're being redone, but that it is something to target and to consider during pregnancy.

But further, when we looked in more detail with Angela Birnbaum, is a colleague who's a pharmacokinetic wizard and modeler, we were able to see two populations, which is exactly what we were noticing in our practice. So it's nice when the data works out with what you notice in practice because some women we were having to increase their dose a lot but some didn't really change.

So it turns out there is about 23% of women have very little-- this is clearance-- very little change in clearance over 40 weeks. But the other 77% of women have this dramatic increase. And if you separate them out from the other group, their clearance increases 219% above baseline. So in other words, sort of three-fold. So you start at 300 milligrams per day at the end of pregnancy, you're going to be at 900 milligrams per day.

So it's really often, if you're not doing this all the time like I am, and thinking about it all the time, it's kind of scary. Like, gosh, that's such a high dose. And you get push back from the pharmacies and insurance company and from the patient. So it really takes counseling, like, this medication level is the same in your blood despite how many pills you're taking. And lamotrigine is particularly extreme compared to the other medications because of its pathway of glucuronidation gets enhanced due to estrogen during pregnancy.

Another thing I forget to mention is I tend to make increases at 100 milligrams at a time. Never seen a rash. So it's something that often is hard, if you're not doing that all the time, to adapt. So it would be great if it was just lamotrigine but unfortunately, it's not. Really, all the medications we're showing this. If the level drops to less than 65% of the baseline preconception level, then the risk of seizure worsening goes up.

So this was a small study from Brigham run by Emma Vainescu, our colleague, and she looked at the other medications, a combination of levetiracetam, carb, phenytoin, topiramate, valproate, and showed the same pattern. If the level dropped to less than 65%, they were more likely to have seizure worsening. So we're starting to look at this in MONEAD.

So as I mentioned, the MONEAD study and just to go over, we enrolled them in pregnancy up until 20 weeks. Earlier is better, of course. And then we followed them throughout pregnancy. Also got a birth visit and then followed them for nine months postpartum. Another control group was non-pregnant women with epilepsy. So we followed them exactly the same way. And we enrolled the non-pregnant women with epilepsy specifically to reflect the pregnant women with epilepsy. So we watched it every week, to balance the cohorts based upon the seizure types, seizure frequency, and what medications they were on.

Because the strength of prospective data is so much stronger in clinical research, and certainly when you go to publish, we used our postpartum as our non-pregnant baseline for the pregnancy. So we did try, actually, to enroll some women prior to pregnancy but it wasn't enough women to be able to do a lot with the data. So this is our non-pregnant baseline as far as seizure frequency, what their medication clearance was, et cetera.

So I'm just going to show a couple. But we were able to show compared to non-pregnant baseline, which is now here in the postpartum, this is what the concentration would be if you didn't make changes in the dose. So we're kind of flipping the idea of clearance. So if you had the same dose-- this is normalized for many things-- but say if your concentration was up here for a certain dose, if you didn't make any changes during pregnancy, in the first trimester it would already be almost half.

So we now know that the clearance and the upregulation of glucuronidation addition occurs so early that when I tell patients, call as soon as you have a positive pregnancy test at home when you missed a period, and call us right away. And then we start doing therapeutic drug monitoring in the first trimester. And then you can see there's differences in the second trimester and then the third trimester.

So levetiracetam, there are differences, already, again by the first trimester compared to non-pregnant baseline. And then I won't show you all of them in the interest of time, but we also have similar findings for zonisamide, lacosamide is one of the first ones, I think. First report on lacosamide topiramate.

Now, the one that doesn't change much has been also reported before-- carbamazepine actually doesn't change that much-- free carb. So if someone is, particularly in a setting where they don't have access to therapeutic drug monitoring, that is one consideration that it could be a preferred medication for focal seizures in some areas of the world.

So also, this is where we went-- when we designed the study we went back to the AAN guidelines and used it to as for-- to design the study. So what were all the things in the AAN guidelines that came out in 2009 that said we don't know, we don't have enough evidence to know the answers to these and how to manage women during pregnancy. And so one of them was seizures. And it said there's really insufficient evidence to determine if there is a change in seizure frequency in pregnant women with epilepsy because there's never been a gold standard comparator group, which is non-pregnant women with epilepsy.

So that's one of the reasons we had the control group of non-pregnant women with epilepsy. And what we were able to see in the pregnant women with epilepsy over pregnancy, 62% maintain their baseline seizure frequency, 23% increased-- and we actually had a very liberal definition of increase. So if a woman had two seizures a month on average and it went up to 2.2, it was called an increase. So 23% of women had an increase during pregnancy compared to their non-pregnant baseline and 14% had a decrease.

But if we didn't have these controls, a lot of things are attributed to, oh, pregnancy causes this, pregnancy causes that. So if we didn't have the controls, we would say, potentially pregnancy causes. But fortunately, we had controls followed exactly the same way and with the same baseline characteristics, and they had the same distribution. 25% of them, you follow them over 9 months with daily seizure diaries which was in an app, and 25% of them are going to have an increase. It's just fluctuation of epilepsy. 65% no change.

So you can see the similarities. But the difference was, is what happened with her medication doses. So pregnant women, 74% of them had a change in dose, compared to only 31% had a change in dose in the controls over that period of time. And again, observational study. We didn't tell people how to manage the women. This was just a practitioner preference. But granted, it was 20 sites across the country that have an interest and expertise in this area.

I personally don't think this reflects what's going on in the rest of the country or the rest of world, but I don't know. So that's potentially a next proposal we're talking about, to really see if there is a difference and how we can now transfer this into implementation science to help sort of all women during pregnancy transition with epilepsy so they don't have to come see Dr. O'Neal or come see me for this.

And then when we looked at specific medications-- this is where I geek out on this stuff-- but how these women were managed. Dose increases are in red. And so during trimester 1, 2, 3, you can see lamotrigine-- all these practitioners were doing this dose increases that follow the changes in clearance that I mentioned.

And then after pregnancy, dose decreases. Levetiracetam similar, but again nothing as extreme as lamotrigine but still percentage increases here around 50%. Levetiracetam, ox carb, similar things, zonisamide. Carb, as I mentioned, is mixed. It doesn't change as much. And then topiramate. And this is the control women and how their doses were managed when they were followed for nine months. So a big difference.

So when we looked for risk factors, we went into the proposal based upon prior literature saying that women on lamotrigine and ox carb were more likely to have seizure worsening, but that is not what we found. There is no difference by regimen or type. And the one thing that has been reported before, if a woman was seizure free in the nine months prior to pregnancy, her risk for seizure worsening was much lower. It was 0.26 risk of seizure worsening compared to the rest of the group.

So we talked about how to increase the medicines. But how do you decrease them? And we do not have evidence-based medicine for this. Going back to the old study when I was at Emory, we just did a [INAUDIBLE] postpartum taper with lamotrigine over 10 days, and we found if the women-- if they were given the taper and communicate well and followed it, they were less likely to have toxicity, versus if they didn't follow the postpartum taper.

And toxicity, it's significant. We cannot definitely minimize that, because they will get diplopia with lamotrigine-- throwing up, ataxic, risk of falling carrying their baby. So it's really an important thing to manage. Now with a pharmacokinetic modeling by Dr. Birnbaum, she showed that the lamotrigine clearance changes to baseline over two to three weeks. So now I do tend to decrease.

What I do is start day three, decrease, and then by two to three weeks out, I want them back to their baseline dose plus 50 milligrams because of sleep deprivation. And then I just kind of work backwards. So if you're going from 600 to 300 and kind of do the stepwise taper every approximately three to four days.

Levetiracetam, because there's not as much of a toxicity, I tend to just make the decreases once a week. And again, getting them back to baseline over about three weeks, because that's when renal clearance returns to non-pregnant baseline clearance. There are some of the cytochrome P450 drugs, the metabolism changes more slowly, we think, such as carbamazepine, phenytoin, so we do it a little bit more gingerly. Well, I never have anyone on phenytoin, I guess. But carbamazepine a little bit more gradually.

But this is actually a new study that we're starting here at Pittsburgh with Dr. Birnbaum. So we will be enrolling women to specifically figure out that early pregnancy and then postpartum, and hope to be able to be up here next time telling you what the evidence is and how we're supposed to be doing it.

So breastfeeding-- so breastfeeding-- sorry, going over time. There's a risk-- or the concern is to continue to expose to medication through breast milk. But we have some reassuring information from the NEAD study that the children who are breastfed had actually higher IQ scores if we combine all the medications together, but also even if they were on valproate monotherapy after adjusting for maternal IQ, socioeconomic status, et cetera.

And this study, those findings were actually supported by another study that looked at autistic traits. So lower risk of autism if the children were breastfed despite the fact that the woman is on medications. I also remind women how low the exposure is through breast milk during pregnancy. It's almost the same, the placental cross, so the fetal circulation has about the same concentration as a mother's concentration.

But when we look at breastfeeding, here's like 20% of mom's concentration. We did heel sticks in the babies in MONEAD. Here's carb-- under 10%-- epoxide. Lamotrigine around 30% [INAUDIBLE] levetiracetam is very low-- surprising. Ox carb, zonisamide, there's only a few children there. So, MONEAD participants.

And so, in summary, this is just my interpretation of where the data is and the safest medications are lamotrigine, levetiracetam-- and we do have also some neurodevelopmental findings from other countries I didn't go in to for the interest of time that place it in a low risk. A little bit higher risk is carbamazepine, ox carb and zonisamide. And the reason why I'm keeping it here is because we do have good neurodevelopmental data on carbamazepine but we don't have it yet on ox carb or zonisamide but we are getting in a MONEAD.

And then higher risk, phenytoin, phenobarbital, topiramate and valproic acid. And then just keeping in mind, this is only nine of our 32-- well, now, probably 34 anti-seizure medicines since I last did this slide. So we have a lot more information to get. And so everyone, thank you for your attention and for contributing to what we do know at this time. So, thank you.