[MUSIC PLAYING]

SPEAKER 1: Thanks, Dr. Waters. Good morning, everybody. I'm going to talk about the management of epilepsy in pregnancy. So just to start out, I wanted to show you how far we've come. The sterilization of people with epilepsy was actually legal in the early to mid 20th century.

So luckily that's not the case today, but even still some women with epilepsy are receiving messages that they should not consider pregnancy. So before I start, I'm just going to get up on a soapbox for a minute and say that as a medical community we should really try hard to eliminate that belief and make pregnancy as safe as possible for women with epilepsy. And that's one of the reasons why we're all here today.

This is the overview, so we're going to talk about things to consider before pregnancy, what to watch out for during pregnancy, and then things to review in the postpartum and breastfeeding period. All right. I have two cases. We're going to just introduce them now, and then keep them in mind as we go through the talk. We'll come back to them at the end.

The first case is a 26-year-old female. She has a history of generalized epilepsy with convulsive seizures and she's presenting for preconception counseling. She currently takes divalproex 500 milligrams daily and is well controlled with her last seizure being more than two years ago. And she previously felt therapy with levetiracetam, lamotrigine, zonisamide, and topiramate.

So the question is, should we make any medication changes? All right. And then this is the second case. 21-year-old female. History of focal epilepsy and bipolar disorder and she's been maintained on divalproex 1500 milligrams daily. And she's found to be about five weeks pregnant.

She's never been on any other medications for epilepsy or bipolar disorder. And so for this patient, should we make any medication changes? So keep those in mind as we go through the talk. Before we get to pregnancy, I just wanted to start with a brief discussion about contraception. So one third of women with epilepsy will say that they've never discussed contraception or pregnancy with their neurologists.

So hopefully they're talking to their OBGYN, but it's possible that they're not talking to anyone about these things. So it's important to remember that seizure medications and OCPs can have significant interactions. And as I'll show you in a minute, depending on the patient's AED, IUDs are sometimes the safest choice for these women.

All right. So this side just reviews the interaction between OCPs and seizure medications. The column on the left is the most important one. These are the drugs that can lower hormone levels and consequently make OCPs less effective. So the ones to remember are carbamazepine, clobazam, eslicarbazepine, oxcarb at higher doses, and Topamax at higher doses.

The column on the right are the drugs that don't tend to have an impact on OCPs. But the thing to remember-- I just want to highlight that for lamotrigine, estradiol can actually lower the level. So if they're on those drugs, you need to keep that in mind. All right. So moving on to preconception counseling.

Fertility is something that will come up-- and questions about that. So the data have really been mixed. And depending on which study you read, you'll get a different answer. I just wanted to show you one study that came out earlier this year. This was the women with epilepsy, pregnancy outcomes and delivery study.

So this was an observational cohort. They did the study at four different academic medical centers. And they compared fertility in women with epilepsy and then control women. They had 197 women total. These were all planned pregnancy.

They had to be enrolled in the study within six months of discontinuing contraception. And what they found-- oh, sorry. And they didn't take all comers for this study. They excluded women who had known in fertility or women who had disorders that could lower fertility, things like thyroid disorders or endometriosis, PCOS. So what they found was that women with epilepsy who were seeking pregnancy and did not have fertility disorders have a similar likelihood of achieving pregnancy, time to pregnancy, and life birth rates compared to their peers who did not have epilepsy.

That was their primary outcome. Some of the secondary outcomes were also interesting. So they found that sexual activity rates and ambulatory rates between women with epilepsy and control women were similar. And they also found that rates of pregnancy were similar between women who had active epilepsy versus controlled epilepsy as well.

All right. So we love it when we get to do preconception counseling, but that's not always the case, because frequently women show up and they're already pregnant. And that's because up to 50% of pregnancies in women with epilepsy are unplanned. That's why it's so important when you're treating these women to really think about the choice of AED, the dose of the AED, and monotherapy versus poly therapy.

The ideal is going to be monotherapy at the lowest possible dose. And because these women can become pregnant at any time, the informed consent for using this AED during pregnancy really needs to happen at the time you're writing the initial prescription for them, whether or not they're considering pregnancy at that time. Remember that most women with epilepsy will need to remain on AEDs during pregnancy. But the thing to remind patients especially is that most children born to women with epilepsy are going to be completely normal.

The other big thing with preconception counseling is folate supplementation. So we've known for years that supplementation provides protection against neural tube defects. And the recommended daily dose for all women of childbearing age is 0.4 milligrams daily. But for women with epilepsy, because certain AEDs are thought to interfere with folate metabolism, we think that the recommended dose should probably be higher than that for women without epilepsy taking medication.

So it's usually somewhere between 1 and 4 milligrams, but we don't know what the exact right dose is. Most people will sort of lean more towards the 4 milligrams, especially if they're on a drug like valproate. And then to further illustrate the benefit of folate supplementation, the NEAD study showed that it can actually lead to higher IQ in these babies. So on this graph the IQ score at six years old is on the x-axis, the y-axis has the drugs they looked at, carbamazepine, lamotrigine, phenytoin, and valproate.

The green circles is the IQ when the mother took folate, red circle is without folate supplementation. So you can see that there's a pretty big significant difference between the two. All right. Finally moving on to pregnancy. So about 4.3 million AED prescriptions are actually written annually for women of childbearing age in the US.

And that's for women with epilepsy, but also AEDs that are prescribed for other reasons. A study in 2012 showed that at least 2% of pregnancies are exposed to AEDs. And they found that AED use during pregnancy has actually increased fivefold between 2001 and 2007. So the use of an AED and the dose at conception really matters because first trimester exposure to some AEDs is what's going to lead to increased risk for a major congenital malformation.

So when we talk about major congenital malformations in this setting, that's including heart defects, skeletal defects, neurologic defects, neural tube defects, and then oral facial clefts. And clinical research in pregnant women is really limited, so the data that we have about this usually comes from pregnancy registries. All right. This table shows data from two of the major pregnancy registries.

The middle column is the European registry. The column on the right is the North American registry. If you look at the bottom you can see why lamotrigine and levetiracetam are our two favorite to use during pregnancy. The rate that's quoted for the general population malformation rate is 2% to 3%. And you can see that for lamotrigine and levetiracetam the rates are around those same numbers or even a little bit lower.

And oxcarbazepine, if you'll notice just above lamotrigine, has fairly good rates as well. At the top of the list is valproate, which we usually consider to be the most dangerous. And that's because that rate of malformation is getting close to 10%. It's been said that you need about 400 cases for a drug to be able to establish that overall risk for major congenital malformations.

And you can see that for most of these drugs, that number, at least with the registries combined, has been reached. In 2017 there was an update to the North American Pregnancy Registry and they added gabapentin, zonisamide, and clonazepam. So for this you can see that the rates are looking pretty low, but we haven't reached that 400 case benchmark to be able to know what the rate, or estimate the rate.

All right. So we talked about the type of AED being important when you're talking about pregnancy. So now we're going to talk about the dose of the AED. This graph really illustrates the dose dependent effects. So the malformation rate is listed on the x-axis. The drugs are on the y-axis again.

And then underneath each drug you can see that there's rates for the different doses. At the top is valproate. And you can see that the increase in the malformation rate with the increase in dose, it almost looks exponential. The thing to remember, though, is that lamotrigine, which we usually consider to be pretty safe in pregnancy, also seems to have a dose dependent effect, so that highlights the fact that you really want to try to get women on the lowest possible effective dose.

All right. So we talked about the type of AED, the dose dependent effect of the AED. Now we're going to talk about monotherapy versus dual therapy during pregnancy. This has been studied and published about a lot. I'm just going to share two studies that were published earlier this year.

They're kind of the newer ones. The first study looked at teratogenicity of anti-epileptic dual therapy. They had 1,700 completed pregnancies, about 1,700. And then 368 of them were on dual therapy. From those numbers they found that the risk of major congenital malformation was 1.6 times more with dual therapy than with monotherapy.

And then breaking that down a little bit. They found that the risk of MCM was actually highest when Topamax or Depakote was used in the dual therapy. And they did not find any MCMs with lamotrigine or levetiracetam dual therapy. The second study is similar, but they added in seizure control as one of their outcomes. So they looked at seizure control and malformation rates.

This one had just over 1,800 pregnancies with 508 of them on poly therapy They found that poly therapy treated pregnancies were less often seizure-free than monotherapy treated pregnancies. And that was true for focal and generalized epilepsies. But that makes sense because the people that are on poly therapy are going to be more likely to have difficult to control or intractable epilepsies.

And then they found that drug combinations with dissimilar and similar mechanisms of action achieve similar rates of seizure freedom, which I thought was interesting. And then they found, like the prior study, that increased rate of malformations were seen when Topamax or valproate was used. And then, finally, they found that the combination of lamotrigine and levetiracetam most frequently was associated with the birth of a normal infant after a seizure-free pregnancy.

So that's sort of the goal. And the gold standard is to try to get people through without seizures and have a normal-- all right. And then two more slides about valproate, just because it's the most dangerous to use during pregnancy. We touched on the structural teratogenicity. And we usually think about neural tube defects with this, but it can actually cause a really broad range of defects, including cardiac problems, cleft lip, cleft palate, and GU abnormalities.

And then in addition to that, there's also a cognitive teratogenesis that you should be aware of. With prenatal exposure, the IQ of these children tends to be 7 to 10 points lower than with other AEDs. And that was from the NEAD study also. And they also-- these kids also have an increased risk of autism spectrum disorder and ADHD.

All right. And then this is one study also that came out earlier this year. It was a population based study that looked at prenatal exposure to valproate and the long term school performance in Danish children. So they had 253 children exposed to valproate and similar numbers that were exposed to other AEDs. And they found that there was a substantial decrease in school performance with children exposed to valproate compared to children who were unexposed to AEDs and then also exposed to lamotrigine.

And that effect was maintained even when mothers took less than one gram of valproate daily. All right. So we just got done talking about how harmful some of these drugs can be, but the problem is that we really have to strike a balance between that and the fact that seizures can also be very harmful during pregnancy. They can lead to fetal anoxia and maternal injury. You can see an increased risk of preterm labor in small for gestational age infants.

It's also been shown that there's developmental delay in these children after five or more tonic clonic convulsive seizures during pregnancy. And the problem we have is that there's few effective alternatives to valproate for the generalized epilepsies. And it may be very dangerous to taper or switch these women during pregnancy. All right. In terms of seizure frequency during pregnancy we'll find that most women with epilepsy do not experience a change in their seizure frequency.

It's usually about 65% to 70% they say don't have a change in frequency. The remainder, about half will have an increase, half will have a decrease in seizures. What we do know for sure is that seizure stability prior to pregnancy will predict seizure control during pregnancy and immediately postpartum. And that was confirmed by the MONEAD study.

This was presented at AEN earlier this year. So they had 351 pregnant women with epilepsy and then they compared them to 109 non-pregnant women with epilepsy. And there's a lot of numbers on this slide. But basically, among the women in the study who were seizure free, they found that the women who had epilepsy-- actually all of these women had epilepsy. So the ones who were seizure free at baseline, those who were pregnant did not have a difference in their seizure frequency compared to those who are not pregnant.

Same thing in the postpartum period, there was not a change in seizure frequency between the postpartum women and the control women. All right. So AED levels during pregnancy can vary. We know that levels of lamotrigine, levetiracetam, and oxcarbazepine will generally decline during pregnancy. And that's because of multiple reasons, but the main reason is that there's increased metabolism of the drugs.

Some other AED levels may also decline. And this is widely variable among women and even with the same women across repeat pregnancies. So that's why we really need to follow the levels closely. We'll get a baseline level pre-pregnancy or in the first trimester, and then in the second and third trimester, we usually follow the levels monthly. And then this slide is just to highlight the pharmacokinetic changes that can occur.

So for levetiracetam and lamotrigine you can see that the increase in clearance can be over 200%. All right. So during pregnancy we'll increase doses as needed to maintain that therapeutic baseline level that you got in the first trimester or pre-pregnancy. And then once the women deliver they generally need to be tapered back down to at least close to their original dose. And that taper is not an exact science.

We know that the renal excretion will return to baseline over two to three weeks. The P450 metabolism returns to baseline over two to three months. And there was a study that showed that a taper of lamotrigine over 10 days reduced post-partum toxicity. All right. And then keep in mind, even though you're tapering these drugs after pregnancy, you might need a little bit higher than their baseline level to protect against things like sleep deprivation in the first one to three months postpartum.

All right. And then I have just one slide about non-pharmacologic adjunctive treatment options of epilepsy during pregnancy. So we really have limited data regarding VNS during pregnancy. They have-- in the European registry there were 26 pregnancies that had a VNS. And they found, based on those 26 pregnancies, that their sample size was insufficient to draw any conclusions about VNS during pregnancy.

They did show a tendency toward increase obstetrical complications. However, that was thought to be multifactorial and more due to the fact that these women had intractable epilepsy and the complications that go along with that. And then the other thing that they said was that there's probably not any VNS related direct teratogenicity. But they couldn't conclude that for sure. I did find one case report of a VNS that was implanted during the third trimester.

Didn't have any complications with implantation. And the patient subsequently had a reduction in seizure frequency and a good outcome. And then I could not find any data about responsive neurostimulation, or RNS, during pregnancy. So that's an area that definitely needs to be studied. All right. Moving on to outcomes. So we know that women with epilepsy may be at increased risk for gestational hypertension, pre-eclampsia, and postpartum hemorrhage.

Also, preterm birth, intrauterine growth restriction in small for gestational age infants are actually more common in women with epilepsy. The problem is nobody really knows why there's this difference in outcomes. Some people hypothesize that it's epilepsy, the disease itself, causing the difference.

Some people will attribute it to seizures during pregnancy. And then others tend towards it being an AED effect. The thing is it's probably multifactorial and a combination of all those things, as well as other factors. So we just have more work to do in this area. The one thing I did want to point out is that the small for gestational age infants and AEDs has been studied. And specifically for zonisamide and topiramate there was a correlation.

And this is something that I've seen clinically-- women that have generalized epilepsy that were on zonisamide or topiramate during pregnancy, a couple of them I've seen they have had small babies, but the thing is that the babies themselves are healthy and they seem to grow appropriately along their curve. So it's not clear to me that we're definitely harming them with the small for gestational age. All right. Breastfeeding, we know it's beneficial.

The 2009 AEN practice parameters summarize the transfer of AEDs into the breast milk, and they used a lot of complicated language. But basically, the gist of it is that levetiracetam definitely transfers into the breast milk in significant amounts, but it doesn't seem to harm the babies. And then some of the other drugs also transfer into the breast milk.

The benefits in this situation generally outweigh the risks. And we really ask mom to just monitor the babies for alertness and for skin rashes. And then this is one thing I found really helpful to share with moms who are considering breastfeeding. In the NEAD study-- found that children with exposure to carbamazepine, lamotrigine, phenytoin, or valproate in the breast milk actually had higher IQs and language scores at 6 years old than children who did not breastfeed.

All right. With post-partum safety there are some precautions for bathing and caring for the baby that we really need to remind moms and families about. So they should use the floor instead of a changing table, stroller instead of a carrier. They should avoid stairs, avoid co-sleeping, anything that's going to-- if mom has a seizure, anything that's going to put mom or the baby at risk we should try to avoid.

Keep in mind that sleep deprivation may increase the risk of seizure in these patients. And they really need a lot of family support and help to kind of avoid that sleep deprivation. So one thing that helps is if they're breastfeeding, if they can pump during the day and let family members help with nighttime feedings and let them sleep through the night. And then finally, it's really important to screen for postpartum depression because it's very, very common and the effects can be devastating.

OK. Back to our cases. So the first one was a 26-year-old. She has a history of generalized epilepsy with convulsive seizures. She's coming in preconception. She's on divalproex at a low dose and is very well controlled. And she previously failed treatment with four different drugs. So should we make any medication changes?

Anybody have any thoughts? Raise your hand if you would try to change her medications. Raise your hand if you would not try to change your medications. Oh my gosh. OK. Let's try again. Hardly anybody voted. Change her medications. Raise your hand. All right.

And if you would not change her medications, what would you do? Yes. Right. I didn't put that in there, but yes. She should be on folate for sure. But in terms of the AED, would you make a change? So yeah. So I would advocate for not changing this patient because she's on a low dose, she's already failed four drugs, and we don't have that many other options for generalized seizures.

And if we try to change her meds at this point, we risk sending her into pregnancy with uncontrolled seizures, which we know can be a really big problem. I don't know if everybody would make that decision, but that would be mine. All right. Second case. 21-year-old female with focal epilepsy and bipolar disorder on divalproex, and she's found to be about four weeks pregnant.

I think the initial site said five weeks. But she has never been on any other medications for epilepsy. So should you change her medications? Raise your hand. Yes. OK. And anybody would not change her medications? No. OK. Good.

So I would try to change her. In this patient, she's four versus five weeks pregnant. It's still early. We might have a chance to change any risk for major congenital malformations. What we definitely have a chance to do is change the cognitive long term outcome for this baby. So something like carbamazepine might be a good choice because you can get the mood stabilization for her bipolar disorder and then also treat her focal epilepsy.

All right. So in summary, many anti-seizure medications can reduce the effectiveness of OCPs. Folate should be supplemented in all women with epilepsy of childbearing age. Levetiracetam and lamotrigine, and probably oxcarbazepine are not associated with increased risk of major congenital malformations. Valproate should be avoided in women of childbearing age due to high rates of structural and cognitive teratogenisis if possible.

Sometimes it's not possible. And then we should monitor AED levels during pregnancy. Women with epilepsy may be at higher risk of complications in the perinatal period. And it's important to address breastfeeding and postpartum safety. That's all I had.