Ruth Adewuya, MD (host):

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This episode is part of our hot topics miniseries, and today I am chatting with Dr. Kimford Meador, who is a professor of neurology and neurosciences at Stanford University, and the clinical director at the Stanford Comprehensive Epilepsy Center. He graduated from the Georgia Institute of Technology and Applied Biology, and received his MD from the Medical College of Georgia. He completed a residency in neurology and did a fellowship in behavioral neurology. Dr. Meador has authored over 400 peer-reviewed publications, and his research interests include mechanisms of perception, epilepsy and pregnancy, preoperative evaluation for epilepsy surgery, and neurodevelopmental effects of antiepileptic drugs, among many others. He has served as the PI for a long-running NIH multi-center study of pregnancy outcomes in women with epilepsy and their children. Thank you for chatting with me today.

Kimford Meador, MD (guest speaker):

My pleasure.

Ruth Adewuya, MD (host):

I like to start these conversations with definitions. Can you define what seizures are and what epilepsy is?

Kimford Meador, MD (guest speaker):

The brain has about 83 billion neurons. It's a very complex electrochemical organ. Sometimes it can go awry, and one of those ways is it can have a seizure. A seizure is excessive synchronous firing of the nerve cells in a pathological way. Depending on where they start and spread, you can get different symptoms. Any brain can seize. 1 in 10 people have a seizure in their life, but most of these are provoked. About 1 in 26 have epilepsy, which is recurrent seizures not provoked by anything that should cause a seizure. At any one point in time, it's 1 in 100, so it's a pretty common disorder. It's not one disease, it's literally thousands of diseases. It can come from congenital malformation, genetic disorders, strokes, tumors, head trauma. All these disorders somehow set the nerve cells up to be more susceptible to firing when they shouldn't be fired, and then synchronizing and firing and spreading.

Ruth Adewuya, MD (host):

In preparing for this conversation, I read about the stigma that has been associated with epilepsy, and that has been carried for centuries, resulting in marriages being outlawed for persons with epilepsy even until the middle of the 20th century in the US. Have you seen the persistence of this stigma in healthcare?

Kimford Meador, MD (guest speaker):

It's much less now that it was. In the middle of the century, there were multiple states in the United States that had forbid marriage if a person had epilepsy. And also, there was even laws to sterilize people with epilepsy. It also used to be, you couldn't drive at all, and that's been revised to a reasonable level where if you got the seizures under control, you may be able to go back driving. But there's still some stigma, and the patients may experience this, that there's a lot of comorbidity with psychiatric disease, and I do think psychiatric stigma is fairly rampant in the United States still in a lot of ways.

Ruth Adewuya, MD (host):

We will definitely be talking about the intersection between mental health and epilepsy later on in our conversation, but since the focus of our conversation is on pregnancy and epilepsy, I wanted to talk about fertility and birth control in patients with epilepsy. Do persons with epilepsy experience higher rates of infertility?

Kimford Meador, MD (guest speaker):

There are reports that have said that they have increased risk of infertility. However, there was a study done by my colleague Page Pennell, recruited women that had epilepsy and women that did not have epilepsy prior to pregnancy, and followed them along, and looked at their fertility rates and problems and that kind of thing. And there was no difference in that group. So, I think there's a lot of women with epilepsy where there's no risk of infertility. There may be other subsets of women with epilepsy that have risks in infertility. For example, women with epilepsy may get polycystic ovarian syndrome, and that's associated with some fertility issues there. But the majority with epilepsy usually have normal rates of fertility.

Ruth Adewuya, MD (host):

When considering birth control, do persons with epilepsy need to consider hormonal options as a potential seizure trigger?

Kimford Meador, MD (guest speaker):

Certainly systemic hormonal birth control, things like birth control pills can interfere with some medicines like lamotrigine, and reduce its level. And some of our seizure medicines like the ones that induce enzymes in the liver like carbamazepine can reduce the level of the birth control pills so they don't work as well. So, in the first case, you lower the lamotrigine, and you may get a seizure. In the second case, you lower the birth control pill hormones and you may get pregnant. What I usually recommend as the best reversible contraception for women with epilepsy is a hormonal IUD, because it doesn't interfere with the medicines of epilepsy and the medicines don't interfere with that.

Ruth Adewuya, MD (host):

You have published extensively on the teratogenicity of antiepileptic drugs. Can you talk about how these drugs adversely affect fetal development?

Kimford Meador, MD (guest speaker):

Yes. They are teratogens as a class. They're all teratogens, they have different severity of teratogenetic risks across the drugs. Interestingly, the risks for teratogenicity for any teratogens drugs was not discovered until the 1960s, after the thalidomide tragedy in the 1950s. People thought maybe drugs

could harm the baby, and then they checked in the epilepsy population. They found there was increased risk of malformations, but it was not til the 2000s that we really started to see differential effects in those malformations with the highest risk being for valproic acid about, or depakene, the American brand name. Around the same time, we had started investigations into this area, in 1999, looking at neurodevelopmental effects. The reason we did that was because we saw animal studies in the '80s and '90s that showed that you could expose the fetus of animals to dosages, teratogens drugs less than those required to produce the malformations that would produce behavioral deficits in the animals, and these deficits appeared to be lifelong.

So, we were worried that the same thing could happen in children. And so we began our neat studies stuff. We followed by second cohort that we're doing now called the MONEAD study funded by the NHS multicenter studies and looking at these issues and our studies along with studies from other places. And in recent years, a lot of population based studies out of Scandinavia and France and other places have confirmed this signal for valproic over and over again. It's very strong signal, it can cause a drop in IQ. It can cause a dose dependent effect on a variety of cognitive measures and it can also increase the risk for autism. It's risk for malformations about 10%. It's risk for cognitive decline is about a 7 to 10 point drop in IQ compared to other any seizure medications and I think a doubling of its risk of autism.

So it has serious problems. That is a drug we don't really like giving to women a childbearing age because of that. The medicine is effective for particular type of epilepsy, a primary generalized epilepsy. Most of those women can be controlled by other medications but some should not. In regards to other drugs and fetal exposure leading to problems with neurodevelopment, we know that there's a couple of drugs that look pretty safe. Lamotrigine and levetiracetam, maybe carbamazepine and its analogs look fairly safe too in terms of neurodevelopment. There's some drugs that have intermittent risks like phenobarbitol and topiramate. And recent publications showed topiramate had risks of intellectual disability and autism and a big population based study from Scandinavia, suggesting that it had risk almost comparable to an outbreak. So we're starting to define some of the drugs that have high risk that we try to avoid.

Some of the drugs that have low risk. Unfortunately, we have over 30 drugs that only a few of them do we really understand well. So there's still a lot of unknowns out there. When I see a woman in clinic and she burned through the first few drugs that are safe, then we're flying blind. It's not evidence based medicine at that point, it's best guess medicine. And we're hoping to get more and more data. Some of the large population registries are showing signals here and there for different drugs, but they haven't been consistent like valproic has been across multiple populations. We need to get that signal across multiple studies to be sure. I think it's important for all this to be done for the woman before she gets pregnant, because half the pregnancy in United States are not planned. You can't wait for the woman comes in and say, "Oh, I'm going to get pregnant." If you do that, you're going to miss opportunity to help about half the kids. So I to do it as soon as I start writing descriptions of women in childbearing age.

Ruth Adewuya, MD (host):

What I heard you say is that sometimes you see patients that burn through the first three drugs that we have some really good data on. Other than discontinuing the medication and moving on to the next line available, are there any ways to mitigate the deleterious effects of these medications?

Kimford Meador, MD (guest speaker):

Not very well. The first line of defense is to plan ahead and try to get them to safer drugs and to lower dosages. We expect most of these effects to be dose dependent and I think hearing drugs are relatively safe. Like lamotrigine have shown dose dependent effects when you get very large samples. Their dose

depend effect as little compared to the dose pin effect that we see for valproic, but it's there. So we try to use the lowest dose possible, protect the fetus, but we got to have a dose high enough to protect the mother and baby from seizures. At the same time, once the baby's born there are no drugs or medical treatments or things like that we get the baby. There are some work trying to develop such things. But the main thing right now is to make an early diagnosis and get early intervention, which can help some. It doesn't usually make big deficits go away, but it may help the kid in dealing with some of these things and get along better at that point.

Ruth Adewuya, MD (host):

Does pregnancy alone carry any increased risk of seizure frequency or increased seizure duration?

Kimford Meador, MD (guest speaker):

No, we don't think so. We actually did a formal study in this, it was published in New England Journal a couple years ago. And we followed women with epilepsy who were pregnant and women with epilepsy who were not pregnant in parallel time. And what we've found was that the seizure changes were no different. They were almost exactly the same numerically in terms of increase not changing or decreasing in women. However, the caveat to that is that across these tertiary centers, that kind of standard care was to monitor the blood levels. Because a lot of these medications changed during pregnancy because the mother's clearance changes during pregnancy and it may double and so the levels may be cut in half. And for example, lamotrigine, levetiracetam to the safest drugs have a mean clearance change during pregnancy to 200%.

But it's quite variable across women. Some hardly change at all, some change 400%. So our approach has been to check the level each month and adjust the dose trying to keep it the level similar to what it was pre-pregnancy that the woman was seizure free pre-pregnancy. And in our study, we saw that we made a lot more changes in dosing in the pregnant women versus non-pregnant women. And then, after the baby is delivered, you have about two weeks to the mother's clearance would go back to normal and we have to down-regulate the dosing at that point. Interestingly, if the woman's seizure free for nine months prior to the pregnancy, her chance of staying seizure free throughout the entire pregnancy is very high, about 90%. We try to work with that. We talk to them about sleep deprivation issues which might trigger the seizures. And so, I don't think there's any increased risk of seizures overall from our study.

Ruth Adewuya, MD (host):

And what about labor? Is there a higher risk of pre-term labor in persons with epilepsy?

Kimford Meador, MD (guest speaker):

It has been reported at some studies, but other studies have not found it. So it's not a consistent finding. We didn't find it in our prospective study that we saw increased obstetrical risk. But we did a study here using the California Hospital discharge records and there was some increase in severe maternal morbidity. And it went from about 2 to 4% so that even at 4%, you got to realize that the huge majority of women with epilepsy still going to have normal pregnancies. And I make a point to talk to them about that, especially in the context of the prior laws and stigma that we had about being pregnant in epilepsy. To make sure that they know that the vast majority of the women can have normal pregnancies and normal children. And so, I try to say that specifically to them so they don't get left for the impression that they should never have children.

Ruth Adewuya, MD (host):

Following the journey of pregnancy into delivery, do infants experience negative health outcomes from maternal epilepsy? You already talked about the teratogenic effects and so excluding that, do they experience any other negative health outcomes?

Kimford Meador, MD (guest speaker):

It's not completely clear. Some studies have shown that they usually tend to be these big population based studies that reported that we did not see it in our study. There is some concern if the woman has a whole bunch of convulsive seizures, they doesn't seem to be any risk to the child if the mother's having smaller seizures like staring seizures with loss awareness or something like that. But if the mothers having repeated convulsions, 10 or more, 1 study suggested would affect the child's ocular. And of course, convulsions also can increase the risk for miscarriage. So we are very attuned and watching out to make sure that we have those convulsions controlled and one or two is not going to affect the child usually. But in late term, there had been reports where someone had a convulsion and fell or had a convulsion in them, had a miscarriage. So it can happen, but I think they're fairly rare events.

Ruth Adewuya, MD (host):

And how about breastfeeding? Does exposure to antiepileptic drugs through breastfeeding carry arrests to the infant?

Kimford Meador, MD (guest speaker):

There used to be people that wrote books and said you shouldn't breastfeed and they should take anticonvulsant drugs. And one of my colleagues had a patient back east, who had a baby and the nurse told her not to breastfeed and the pediatrician told her not to breastfeed, then got a consult and neurologist told her not to breastfeed. She determined breastfeed. So she breastfed then they reported her to social services for child neglect and she came to see my friend and she had to help fill out forms and clear her of any problem. The real truth is that there's about three studies now that show no risk whatsoever and women that are taking that. Large population based study from Norway and our study showed no risk at all at three years of age. And then we actually showed the children that breasted actually did a little bit better in cognition than the children who didn't get breastfed.

And we know that there's all these positive effects to both the mother and child from breastfeeding. And recently, in our recent Coast Heart, we looked at the levels in the child, people measured it in the milk and this and that. But we measured actual levels in the child, and in the mother when they're getting breasted. And we found that the levels are generally very low. Almost all of them are less than the mother's level. So they've been exposed for nine months at a level that is the same as the mothers. We know that those levels from cord blood are exactly the same as the mothers. So they've been exposed for nine months there. So there's been damage that's already happened there. And so they're not getting exposed to very much and we don't see any adverse effect. And in our six year old group, we actually saw a slight increase in IQ over the group that was breastfed. So more evidence that encourage women to breastfeed if they want to.

Ruth Adewuya, MD (host):

What are some specific recommendations for breastfeeding?

Kimford Meador, MD (guest speaker):

Yeah, I think that revising the new set, they've used to say we're not sure and then, now, revising the set of recommendations. My recommendation is to breastfeed if they want to. The only possible exception would be if they hadn't been on medicine all during pregnancy and now they got started in the postpartum on a medicine that is one of the ones that's dangerous, not want to do that. But even then they're going to get exposed to pretty low levels. But if they were already exposed, any damage to drug cause is already happening. We're not seeing any increased risk of that in the breastfeeding.

Ruth Adewuya, MD (host):

I would like to go back to the comment you made earlier in our conversation about the comorbidities with mental health issues. Do women with epilepsy experience an increased risk of postpartum psychiatric disorders or framed another way? Do expectant mothers with epilepsy experience higher rates of depression and or anxiety?

Kimford Meador, MD (guest speaker):

Yes. Our study also addressed this recently published a paper about this looking at major depressive disorders diagnosed by gold standard SCID diagnosis. And then, we also used a variety of standardized forms to look at symptoms for depression and symptoms for anxiety. And we were comparing health in mothers that were pregnant and in the postpartum and we compared it also to the non-pregnant parallel group. And what we found was is that the woman of epilepsy who were pregnant had increased risk for depression and anxiety during pregnancy in the postpartum. So it's a double whammy, we know that people with epilepsy have increased risk for depression, anxiety. We know that women who are pregnant that don't even have epilepsy have increased risk for depression, most emphasizes the postpartum depression. So you put those two together and maybe, it's not surprising that the women with epilepsy have an increased risk.

I think our mothers did well but they were in a very special group. If someone doesn't pay attention to this depression thing and don't get it treated, which is usually by psychological therapy rather than drugs, we try to do that especially during the pregnancy itself, trying to reduce the number of exposures. Our group did quite well. It's interesting that we asked the question about whether the mother's mood affected the kids' outcome. And we analyzed all this and the one feature that popped out of our analysis was anxiety in the postpartum, it was related to more cognitive performance, and the children at three years of age. We're still following the kids. We'll go to six eventually, but right now we just finished through three years of age in terms of sending in publications.

And that's very interesting to me, because I've always felt women with epilepsy are always a little more nervous about their pregnancy, especially if their first pregnancy. I told people my main job is try to reassure them and reduce their anxiety and worry that things are going to be fine. I spend a lot of my time that way. I tell them about the risk but then, I'm trying to put it in context. And now, tell them if you're having anxiety, it's very closely interlinked with the depression. They have either one of these, we need to know about it and that we need to take step to try to make it better. Because that's going to not only help them, it's going to help the baby too.

Ruth Adewuya, MD (host):

Following up on that, does the epileptic community experience disability health disparities in pre and postpartum care? And if so, what steps can be taken to provide equitable care for those with epilepsy?

Kimford Meador, MD (guest speaker):

The question is good, but trying to solve the problem is hard. I do think even if you're not pregnant, there's healthcare disparities in epilepsy, especially in regard to psychiatric care. As I mentioned, there's a higher comorbidity for depression and anxiety and people with epilepsy irrespective or whether they're pregnant or not. And then, trying to refer those patients to get psychiatric care can be different, especially if they're from low socioeconomic status and they don't have very good insurance. It can be quite difficult and their only recourse might be to go to the county health department. Some county health departments are quite good, others are fairly visible and it is difficult trying to do that. And our patients come from broad distance and so, I have to try to figure out how to interact or get their local doctor involved to try to help them find these resources.

It is striking to me that I have quite a few patients that referred to me and the insurance covers the evaluation for epilepsy. And then, I can't refer them across the street to my psychiatric colleagues to get the care that they need for the depression or the anxiety. It's very frustrating in that regard. So yes, there are disparities. What steps can we take to improve those? At my level at this point, it's less than adequate. I feel like I try to do the best I can to try to find them care and talk to them about go back to your insurance, see who is on the list. If they don't have anybody, then go see your local mental health thing. I try to explain to them that it doesn't have to be a certified psychiatrist, psychologist. There are some therapists out there that can help them. For some things like anxiety, there's therapies you can use that don't require a healthcare referral.

Things like mindful meditation or yoga, progressive relaxation techniques such as Tai chi, all these things can help with these kind of psychiatric symptoms. This needs to be something that ultimately needs to be addressed on a national level. The countries don't have the fortitude or concern to act on this at this point. So it remains a problem within our healthcare. And I do think that the concerns about disparities has really peaked in the last few years. It's been there a long time and what's encouraging is the concern about it has peaked in the last few years. The last big neurology meeting, there were multiple lectures about disparity issues.

Ruth Adewuya, MD (host):

It's encouraging that as we look towards the future that these things are being talked about and that hopefully, some tangible things will be done around the issue. But along the same vein as looking into the future and the world of pregnancy and epilepsy, what is still not well understood regarding pregnancy and epilepsy?

Kimford Meador, MD (guest speaker):

A whole much. I would say the major issues to me are about the teratogenicity in this regard, especially the developmental teratogenicity. As I mentioned before, we have a handful of drugs, five to eight that we understand well is whether dangerous or not high risk or low risk and a whole bunch of others we don't understand at all. Because we don't have human data monitoring those, we don't have the animal data that least gives us the windows to where they might be potentially problematic. Sometimes we can see that until the animal studies they draw the levels, you can see where the stacks of the nervous system start to kick in. For example, for valproic, they again below the therapeutic range that we used for epilepsy. And I have carried two women through pregnancy, who were well below the therapeutic range but that seem to be enough to control them. And their babies did well.

They came to me pregnant on valproic some years ago. Luckily, the use of valproic has fallen off dramatically in the United States. So we don't see as many now at all that way. So that's, good. People have generally gotten that message but now we're working to get more information, because as soon as we get more information we can guide the pregnancy much better than what we can do right now. In

addition, I would say that we need to understand these mechanisms better. And there's a very pertinent article just published this summer in brain looking at valproic mechanisms. And it was fascinating to me that what they had used an animal model, what they were showing is that the drug was altering the genes. It was down legging genes that were important for synaptics epigenesis and for cell neuro growth.

And they were also uploading some genes that are related to intellectual disability or schizophrenia. So probably this is how it happens. It has this epigenetic kind of effect and that really impairs the brain of the fetus through life similar to probably what alcohol does too. Some of the anticonvulsant drugs and alcohol can kill neurons in the immature brain because there's not that many nerve cells that die. So it's what's happened to the remaining nerve cells that sit after and such. So understanding that how in a dose manner for across drugs and understand what dosages do it for a drug would help us guide, help us look more specifically to drugs that we saw were risks or trying to avoid those. They're trying to get more data on those to understand that and improve our care and when with epilepsy, also doing the animal studies helps us understand possible mechanism that could be interceded on and maybe develop mitigation treatments or blocking treatments to try to improve the outcomes in these children.

And finally, teratogens work in a dose dependent way. We see that many ways that our anticonvulsant drugs, but they also work in a susceptible genotype and we don't understand the susceptible genotype yet. And we have a long way from understanding of that about all we understand if a woman has a malformation and one pregnancy, she stays on the same drug, her wrist and a second pregnancy, it is high. And if she has no malformations in one pregnancy, her risks of malformations is lower, she stays on the same drug. So they're clear indication, there's a genetic component there which we know that exists for teratogenic. But we don't know those risk genes and that might allow us to not only predict risk for different drugs. But also again, may give us clues about research techniques that might be used to help block or improve the brain function than people with a susceptible genes.

Ruth Adewuya, MD (host):

As you look at the current landscape of research that's happening in this area, what are you looking forward to seeing? What makes you excited about the potential of improving care in this field?

Kimford Meador, MD (guest speaker):

In the last few years, the things that have encouraged me the most are that the results from our study, which we've had a bunch of papers and this prospective study. The prospective study is like we have a few and far between. But we've seen a lot of reports of population based studies out of Europe and some for malformations out of the US too. Those are encouraging that more and more people are recognizing this problem than it is one of concern. It's a big chunk of our population to just say, all right, this isn't important because just a women's issue. It's not a women's issue, husbands, fathers are just as concerned and the children that get these problems. Obviously, they're bearing the blunt of this, but to think about the pathos of the disease and you expand it into the next generation is horrifying.

I hope that people that do the funding, whether it's in US or Europe or UK, will recognize this and try to address this issue through initiatives to look at both the basic science and the human data to try to understand this better. I think we can do a better job of recognizing these things, getting information more quickly and therefore, avoiding more kids getting exposed needlessly to drugs that are going to hurt them.

Ruth Adewuya, MD (host):

My final question before I let you go is advice that you can give to clinicians who are not epilepsy experts like yourself and are navigating the complexity of caring for pregnant people with epilepsy. What advice or what takeaways would you have for them?

Kimford Meador, MD (guest speaker):

I would say to inform women about this early, which you're writing the drug, you better be informing them about these risks and tell them about which drugs or risk or which or not. And there are some good publications out there. Dr. Lee and I have recently published a review in neurology continuum that reviews all this, but this several other good reviews out there. So if you're taking care of these women just like I do when I get a disease, I don't know much about it. I go and read about it and try to find out more so I can do my job better. If it's too complex, some women are very complex, then maybe they felt all the good drugs and now what the hell do you do? I would have a low threshold to refer them to out, just talk to someone who knows more about this. And I would encourage them to, one point I've not made today that's very important is that women of childbearing potential in these medications should be on folic acid.

And I think they should just be constantly on it during their childbearing years until they go through menopause or have a hysterectomy or the husband has the tumor ligation, they should be taking folic acid. Now we know in the general population, folic acid reduces malformations and women with epilepsy, it doesn't look like it blocks the malformations that are related to the anticonvulsant drugs, but it does improve language outcome and reduce the risk of autism. So that's, a big reason to be taking a folic acid. The exact dosing quite right for healthy women we say 0.4 milligrams. And for women with epilepsy, I give a little bit more, at least a milligram, but the data for that is not very good. I would not give more than four milligrams because there's some studies suggest that might have an increased rest for behavioral problems. So somewhere between one and four milligrams, they should be getting per conceptual folate, because the folate exposure about the first eight weeks is very critical.

Sometimes women don't even know they're pregnant for a big chunk of that and that ever week that goes by is a less chance to get the per conceptual folate. And it's been shown to improve cognition in children only with epilepsy. And so, I think that's an important message. Try to pick a drug that works, but one that has lower risk and try to use the lowest dose possible to get complete control of the seizures, especially the convulsions. Those would be the main messages and I would recommend that they monitor the level monthly so that they can adjust the dose and remember to adjust it back down after delivery.

Ruth Adewuya, MD (host):

Excellent. Thank you so very much for taking the time to chat with me and sharing your insights with us on this topic. This episode was brought to you by Stanford CME. To claim CME for listening to this episode, click on the claim CME link below or visit metcast.stanford.edu. Check back for new episodes by subscribing to Stanford Medcast, wherever you listen to podcasts.