Melanie Cole, MS: Welcome to the podcast series from the Specialists at Penn Medicine. I'm Melanie Cole. Joining me today is Dr. Genna Waldman. She's an assistant professor of clinical neurology at Penn Medicine, and she's here to highlight epilepsy in women of childbearing age with a focus on reproductive health. Dr. Waldman, thank you so much for joining us today as we get into this topic. Can you speak a little bit about the prevalence of epilepsy, the age it tends to present the most often, and what you've seen in the trends?

Genna Waldman, MD: Thank you so much for having me today. This is a really important topic and I'm really happy to be here. The prevalence of epilepsy is about 4-10 in a thousand people, and it really affects people across the lifespan. Although there's peaks in childhood and older adults, it really is a lifelong disease. So thinking about women through their reproductive years is a really important time and an important topic to discuss.

Melanie Cole, MS: Well, we know that hormones and anti-seizure medications can have varied effects across the lifespan, and this may affect sexes differently. What are some important interactions to highlight when approaching hormonal health in your patients with epilepsy?

Genna Waldman, MD: Hormones such as estrogen, progesterone, testosterone can impact epilepsy and they can interact with a variety of anti-seizure medications. For people of female sex, variations in their hormone levels throughout their menstrual cycle can affect their seizures. And about 30 percent of females with epilepsy are known to

have a type of epilepsy called catamenial epilepsy, in which seizures occur more often during specific time points in their menstrual cycle.

When we ask patients to keep a seizure diary, it can be helpful for them to also track their menstrual cycle to look for patterns, and that's because we have certain treatment strategies to address this. Such as using Depo-Provera injections with the goal of anovulation, if during the estrogen peak of ovulation there's an increase in seizure frequency that's seen. Or increasing medications empirically during the menstrual week, if during that time period we reliably see increased seizures.

Another time point during the lifespan is menopause. There's a known risk of early menopause in females compared to healthy control populations. And in addition, we can also see seizure rates increase during that menopause period. People and providers often hold a misconception about not using birth control or hormone medications if they have epilepsy, and while it's true that anti-seizure medication interacts with hormone medications, most are safe to use, and which medications to use should really be a discussion that includes your neurologist.

There are some anti-seizure medications that are known to be enzyme inducers, and they may decrease the effectiveness of birth control, including oral pills, implants, and vaginal rings. It's really important for patients and their providers to discuss their birth control medications with their neurologist or epilepsy doctor. Overall, an IUD is generally the one we recommend most. A small study shows that stable hormone levels are seen, expected uterine lining changes are seen, and there's a decrease in bleeding events independent of the type of anti-seizure

medication supporting its efficacy for using that as a good birth control method.

But there are several medications that we have available to us that don't impact the efficacy of birth control. And so all people of childbearing ability, and if a provider is taking care of one of these patients, should have a discussion, including their neurologist on what birth control methods can allow for safe pregnancy planning and planning for pregnancy prevention. I also want to make a comment on undesired pregnancies and medical options for treatment. Plan B is also a hormonal medication and the Plan B dose is high enough that we assume it won't have an interaction with their anti-seizure medications. But we have no medical studies on this.

So if a patient is on an enzyme inducing medication to ensure the efficacy of Plan B, it may be advised to take two doses. Similarly, the medications used in home abortion, mifepristone and misoprostol, are medications we don't have specific data on how that and their anti-seizure medications interact. We know that they're safe and that they are effective and they shouldn't have an interaction with the patient's anti-seizure medications. But if using those treatments, of course, we'd want patients to work closely with their OB/GYNs.

We have limited data on gender affirming medications in the transgender population with epilepsy, and most of our data is extrapolated from women and birth control studies. But similar to birth control medications, if an individual is on an enzyme-inducing seizure medication, it may decrease the effectiveness of their hormonal gender-affirming treatment. Including your neurologist in the discussion of your

epilepsy medications is really what is recommended so that we can find effective seizure medications that don't impact their transition.

Melanie Cole, MS: Dr. Waldman, what do you recommend for people with epilepsy who are beginning to think about starting a family? Tell us a little bit about pregnancy planning, fertility issues, and any of the questions that you hear from patients on a regular basis?

Genna Waldman, MD: This is such an important topic, and I think both providers and patients have a lot of questions around family planning and pregnancy. Is it safe for them? What will happen with their epilepsy? Are there risks to the baby? I think the first question is about fertility and infertility. Being evaluated for infertility by an OB/GYN is always recommended and should be a part of care for patients. People that have epilepsy who are assigned female at birth are known to have higher rates of polycystic ovarian syndrome and that may impact fertility.

The WEPOD study or the Women with Epilepsy: Pregnancy Outcomes and Deliveries study that was published in JAMA Neurology in 2018, is really one of our best studies and the first prospective study that compares women with epilepsy compared to healthy controls without known reproductive endocrine dysfunction. And this study found comparable likelihood of achieving pregnancy, time to achieve pregnancy, miscarriage, and live birth rates. This is really encouraging data for us because before this, there were studies of conflicting reports of increased infertility and birth rates in people of childbearing age with epilepsy.

The takeaway from this is that people of childbearing ability with epilepsy are expected to be able to get pregnant successfully. However, fertility is a really complex issue and there may be other medical comorbidities independent of their epilepsy. So it's really imperative to also have a consultation with your obstetrician and gynecologist. We know that when people are diagnosed with infertility and undergoing fertility treatments, we have one small study that showed similar rates of live birth to embryo transfer compared to those without epilepsy. Again, this is really encouraging data.Estrogen, however, can decrease lamotrigine levels. So specifically if your patients are on that medication, they may need adjustment in their seizure medications to keep them seizure free during fertility treatments.

I'd like to make a small point on men with epilepsy. We have very limited data around this area. However, there are a few studies that show the medications that are enzyme inducers may also affect men's testosterone levels and their sexual function. We have many studies using survey data that show an increased rate of depression and anxiety in men with epilepsy and that it is associated with sexual dysfunction. More research is certainly needed in this area. But it does emphasize that we should also be discussing this topic with men with epilepsy and not just women.

Now I'd like to move forward to discuss and focus a little bit about the time of pregnancy. About 50 percent of pregnancies are unplanned in patients with epilepsy and complications such as interuterine fetal death is higher in unplanned pregnancies. So this really emphasizes that we need to be talking to our patients about this and counseling them. There are important risk and safety guidelines that are very specific to people

with epilepsy while they're pregnant, and having that time prior to conception allows us to optimize epilepsy treatment and have important conversations with patients.

Epidemiologic studies do report high maternal death in patients with epilepsy if they have poor seizure control, medication non-compliance, and are not triaged to high risk obstetric care. So comprehensive obstetric care is a critical part of this. There are higher rates of pre-eclampsia, labor induction, and C-section in women with epilepsy, but I do want to emphasize that 90 percent of all pregnancies result in delivery without complications.

A big question that providers and patients ask is what will happen to my epilepsy during my pregnancy? A landmark trial published in the New England Journal of Medicine in 2020 from the MONEA Group, which is the Maternal Outcome of Neurodevelopment Effects of Anti-seizure Drugs, evaluated both women with epilepsy, pregnant, and matched women with epilepsy who were not pregnant over two 9-10 month periods. Reassuringly, this study found that seizure frequency did not change during pregnancy. Furthermore, patients who were seizure-free for nine months prior to their pregnancy were more likely to remain seizure-free during pregnancy. Seizures during pregnancy are associated with a risk of preterm delivery, small for gestational age babies, and there's a risk of decreased IQ in children of mothers who have frequent convulsive seizures.

So this really emphasizes the importance of pregnancy planning and achieving optimal seizure control with your epilepsy physician or neurologist prior to your pregnancy. Out of the same study group, a

separate study published in JAMA Neurology, just this past year (2022), is the most robust study investigating anti-seizure medication levels throughout the pregnancy period. We know there are several factors that impact anti-seizure drug levels throughout pregnancy, including changes in metabolism, renal blood flow, albumin concentrations, and morning sickness.

This study provides evidence that medications such as lamotrigine, levetiracetam, lacosamide, carbamazepine, and oxcarbazepine had decreased levels throughout the pregnancy. We recommend during preconception to obtain levels. As the goal throughout the pregnancy would be to maintain seizure control using the pre-pregnancy levels as a guide, expecting that we need to increase the medication dose, but limiting the need for unnecessary increased exposure when able. It is also recommended to check levels throughout a pregnancy, at least every trimester and at times up to monthly.

Limiting unnecessary exposure is important in mitigating the risk of fetal development and teratogenicity. This is a big question that providers often have as well as patients when they come see me in the office. There is a need for more data on newer anti-seizure medications. However, there are some important safety concerns we are informed about. The rate of major congenital malformations in the general population is around 1-2 percent. The MONEA study reports that women with epilepsy do have higher rates of major congenital malformations and fetal death overall, although this finding was not statistically significant, and again, 90 percent of pregnancies are successful and healthy.

We know that medications such as valproic acid, phenitoin, carbamazepine, and topiramate have higher rates of major congenital malformations, and we advise against using those during pregnancy. In addition, if women are on multiple anti-seizure medications, they are at higher risk. We have reassuring data on lamotrigine, levetiracetam, and oxcarbazepine from our registry data. We now have information on the development of children from women with epilepsy up to eight years after birth. Medications that are known to impact IQ and cognitive development include valproic, acid, topiramate, and possibly carzomazapine.

We have reassuring data on exposure from lamotrigine, levetiracetam, oxcarbazepine, and zenicimide, as well as using folic acid supplementation, independent of which anti-seizure medication they are on. There are many other medications for epilepsy that women may be on to control their epilepsy. This is a complex discussion when patients are on medications where we have no data. However, in general, control of epilepsy and decreasing the risk of seizures is an important factor in that decision.

I'd like to also mention breastfeeding as this is a question providers and patients often come to my office asking about. Breastfeeding is an individual decision that should be made in collaboration with the family, your OB/GYN but also including your neurologist. Postpartum women with epilepsy breastfeed less than those without epilepsy, although that increases just by a neurologist providing proper counseling. There are several studies now that show that infant exposure through breast milk of anti-seizure medications does occur, but is significantly lower than the exposure intrauterine, and often below lower limits of quantification. So

it is the recommendation of the American Academy of Neurology and the American Epilepsy Society that postpartum women should breastfeed if able, in particular, their epilepsy should not be the reason to not breastfeed.

Melanie Cole, MS: Thank you for that comprehensive answer, Dr. Waldman. As we wrap up, I'd like you to speak about resources that you would like patients and providers to know, for people that have epilepsy of childbearing age. Tell us about the Epilepsy Pregnancy Pathways program at Penn Neurology and your multidisciplinary team

Genna Waldman, MD: The Penn Epilepsy Center has providers, including all of our physicians and nurse practitioners, who are experts at preconception, intrapartum, and postpartum counseling. They help provide an individualized approach to the care and guidance of epilepsy throughout the pregnancy time period. In addition, we have a world class obstetrics department whom we have close collaboration with. As well, we offer genetic testing and counseling to any patients interested, whether they're pregnancy -planning or not.

Another resource that I would want providers and patients to know about is that you can find good resources at the Epilepsy Foundation of Eastern Pennsylvania. Lastly, when our patients do become pregnant, we recommend that they all enroll in the North American Pregnancy Registry as this has been the driving force for all the information we have around our treatment and guidance for patients and providers.

Melanie Cole, MS: Do you have any final thoughts for referring physicians and when you feel is the best time that they refer to the Penn Epilepsy Center?

Genna Waldman, MD: Early referral is always encouraged. If a patient with epilepsy is considering starting a family, I recommend they discuss this with their neurologist or epilepsy doctor as early as possible, and for providers to refer their patients to us here at the Penn Epilepsy Center. As well as mentioned throughout this podcast, it's not only about pregnancy, but discussing birth control and interactions with other hormonal medications, whether or not the goal is pregnancy or pregnancy prevention. Lastly, I want to reinforce a positive message about pregnancy and epilepsy. It is safe, but requires the proper guidance and including a neurologist or epileptologist is imperative for a happy and healthy pregnancy.

Melanie Cole, MS: Thank you so much Dr. Waldman, for joining us today and to refer your patient to Dr. Waldman at Penn Medicine, please call our 24/7 provider only line at 877-937-Penn, or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient. That concludes this episode from the Specialists at Penn Medicine. Please remember to subscribe, rate, and review this podcast and all the other Penn Medicine podcasts. I'm Melanie Cole.