Women's Health
Complex Interactions of Epilepsy, Medications & Hormones
Webinar
(Transcript)

Dr. Laura Lubbers: 00:00 Welcome everyone to today's webinar. I'm Laura Lubbers, and I'm the Chief Scientific Officer at CURE Epilepsy. I want to thank you all for joining us today. As a part of our recognition of women in March, today's webinar will focus on women's health, specifically the complex interactions of epilepsy, medications, and hormones. This webinar is part of CURE Epilepsy's 2021 Leaders in Research webinar series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded and can be accessed for later viewing on the CURE Epilepsy website. You can also now download transcripts of all of our webinars for reading.

Dr. Laura Lubbers: 00:42 Our mission is to find a cure for epilepsy by promoting and funding patient-focused research. CURE Epilepsy provides grants to support novel research projects that advance the search for cures and more effective treatments. In 2020, we launched our CURE Epilepsy catalyst award to help accelerate the basic research we've traditionally funded into the next stage of development and prepare potential new treatments for clinical trials. Today's webinar, we'll discuss how epilepsy and anti-seizure medications can affect hormones and reproductive health. And in turn, how sex steroid hormones can affect anti-seizure medications and seizure control.

Dr. Laura Lubbers: 01:24 We'll also discuss the menopausal transition and how it affects epilepsy. And viewers will also learn about potential treatment options for catamenial epilepsy. Today's webinar is presented by Dr. Page Pennell. Dr. Pennell is a professor of neurology at Harvard Medical School. She is vice chair of academic affairs in the department of neurology, and director of research for the division of epilepsy at Brigham and Women's Hospital, with a secondary appointment in the division of women's health, quite a role. She is a clinical investigator with a focus on sex specific outcomes in epilepsy. Dr. Pennell's current clinical studies focus on the effects of hormones on seizure provocation, pharmacokinetic changes of anti-epileptic medications in response to hormones or differing reproductive phases and maternal and fetal outcomes during pregnancy in women with epilepsy.

Dr. Laura Lubbers: 02:22 Before Dr. Pennell begins, I'd like to remind everyone to ask questions. You may submit your questions anytime during the presentation by typing them into the Q&A tab, located at the bottom of your Zoom panel, and then click send. I know a

number of people have already submitted questions in advance of today's webinar, and we'll do our best to get through as many questions as we can. We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. With that, I'd like to turn it over to Dr. Pennell.

Dr. Page Pennell: 02:58 Thank you, Laura. And thank you for everyone joining us today for this topic. You already heard about the learning objectives, so I will move ahead from that slide. This is a slide, actually the research nurse I worked with in the epilepsy clinic gave me, and it always sort of reminds me, why are we spending this amount of time on issues for women with epilepsy? It's not that men are not as equally important, obviously, who live with epilepsy every day. But there are a lot of extra considerations when treating women with epilepsy, or if you are living with epilepsy as a woman during different reproductive phases that we'll focus on today.

Dr. Page Pennell: 03:49 First of all, one of the things people ask me is does expression of epilepsy in and of itself differ by sex? There's not a lot of difference by males, females as compared to some other chronic disorders, but there still are ones that are noteworthy. It's very common that epilepsy can begin during puberty, and this is more likely to occur in females than in males. When evaluating someone with epilepsy, I always ask them, "When was your first period? And when was your onset of seizures?" It's very frequent to have a correlation between the two or within six months of the two. The other thing is that the hormones that you'll hear a lot more about have direct effects on the brain, which makes sense.

Dr. Page Pennell: 04:36 There's a lot of things we've known long about, such as premenstrual syndrome, that is not just made up. It is because there are effects of the fluctuating estrogen and progesterone on brain activity. Therefore in women, because they fluctuate throughout the menstrual cycle, we can see the effects more clearly than we could in a man who has sex steroid hormones which are consistent and do not fluctuate on a monthly basis. You will hear a little bit more about one third of women are sensitive to hormones. This term is catamenial epilepsy, and it's not a different epilepsy syndrome. We still think about the syndromes, does someone fit the criteria for juvenile myoclonic epilepsy, temporal lobe epilepsy, absence epilepsy, et cetera. But when we use the word catamenial, it just means they have fluctuations in their seizures according to their menstrual cycle. I will go into that in more detail.

Dr. Page Pennell: 05:34 We also see changes in seizure frequency during pregnancy and post-partum and we see change in seizure frequency during the menopausal transition. We also can see the effect of hormone therapies on seizure frequency. We do have a lot of clinical evidence of the influence of these sex steroid hormones, estrogen and progesterone primarily, and their metabolites, called neuroactive steroids, on the expression of epilepsy. Unfortunately, it's very complicated, and this is a very oversimplified diagram. But to think about some of these interactions. I think everyone understands that, I'm going to use the word anti-epileptic drugs (AEDs) but this is often a term, anti-seizure medicines now. But AEDs, and the concentrations in the bloodstream, of course affects epilepsy and seizure control.

Dr. Page Pennell: 06:30 However, epilepsy and seizures, a brain disorder, can affect, potentially, sex steroid hormones and possibly fertility. I'll go into more details on that. The hormones themselves, as I mentioned, have a direct effect on the brain and can affect seizure provocation. Then to make it even more complicated, hormones can affect AED concentrations and our medications we use to treat epilepsy can affect hormones and fertility. Trying to untangle that in humans can be quite difficult, but it is worth considering because it really gives us another avenue to develop personalized medicine treatment strategies, as well as clues to other therapies we can use to help with seizure control.

Dr. Page Pennell: 07:21 Just to go back to the basics, in the brain, at the bottom of the brain, sits a hypothalamus, which is here. Then it connects directly to the pituitary gland. The hypothalamus sends out a signal, GNRH, releasing hormone, to the pituitary gland, which then sends out signals through these pathways, FSH and LH, which have effects on the ovary, which releases the estrogen and progesterone. That has a feedback cycle on the pituitary, but also as I mentioned, up on the brain directly. You can imagine, for instance, one of the common forms of epilepsy, temporal lobe epilepsy, the temporal lobe sits right next to this hypothalamus. Some studies suggest that even having temporal lobe epilepsy on the left or the right has different effects on the function and the secretion rates from the hypothalamus and the pituitary gland.

Dr. Page Pennell: 08:25 What about sexual function and fertility in women? This is something that I became particularly interested in. When you look at reports out there, it really varies quite a bit. Some reports say that women with epilepsy have only 25% of the birth rates compared to the general population. But other studies suggest it's actually the same as the general population, or the same as their siblings. It's not surprising that it's likely

multifactorial. There are reports that in temporal lobe epilepsy, there are more cycles where an egg is not released, called an anovulatory cycle. Therefore a woman cannot get pregnant during an anovulatory menstrual cycle. That's reported to be increased in temporal lobe epilepsy, and also in idiopathic generalized epilepsy.

Dr. Page Pennell: 09:20 Another area that has actually had several studies by Isojarvi and Herzog, I think the bottom line is pretty sorted out now, that polycystic ovarian syndrome is a reproductive disorder where there may be extra cysts. But really it's actually characterized by other things including more anovulatory cycles: more cycles that do not release an egg. It's also associated with weight gain and increased hirsutism, which is a male pattern of hair population. Polycystic ovarian syndrome has been associated with epilepsy. But more specifically, the idiopathic generalized epilepsies, and if they started at younger age of onset, and if a person was treated with valproate early on, or later.

Dr. Page Pennell: 10:16 As hard as many human studies are, it's hard to sort out which came first. But all of these different things increase the chance of having a polycystic ovarian syndrome. Other studies have suggested that in women with epilepsy, menopause transition begins earlier and is more likely to begin earlier with increased seizure frequency. How do we untangle that? Going back to the fertility question, a population-based study in Finland reported that birth rates were lower in women with epilepsy than the general population. So 88%, 88% of the general population. Then other studies, when you look at tertiary referral epilepsy programs such as at a university, where you tend to have patients with a higher seizure frequency. In that case, they said actually the birth rates to women with epilepsy were much lower, 16.9 to 22.5 per thousand, versus women without epilepsy, 67.6. you can see, about a third of women without epilepsy.

Dr. Page Pennell: 11:27 This kind of indicates that there is something about the epilepsy severity and the seizure frequency. There's also many other reasons that birth rates could be low. Overall, there do tend to be lower marriage rates, if you look across all women with epilepsy with many different types of epilepsy. There also are reports of low libido, so decreased sexual drive. Then as I mentioned before, some reports of low ovulation. Some cycles without ovulation. But most importantly, the self-directed decisions cannot be excluded. A survey from Epilepsy Action in the UK found that 33% of the women they surveyed considered not having children because of their epilepsy.

Dr. Page Pennell: 12:13 How do you sort out all these different things? One thing we've decided to do, and with my colleagues, Dr. French, Jackie French, and Dr. Harden, is what about when that person comes to our clinic and they say, "I want to become pregnant, what are the steps that I need to do? And what are my chances of becoming pregnant?" So we designed a study where we took some of these factors out, which is self-decision making, and we took women who wanted to become pregnant and compared them to women without epilepsy who are also trying to achieve pregnancy. Some of you might even, on this webinar, have been a participant. For those of you who have participated in this study or any study, I just want to take a moment to thank you. Because we would never have any of this information without patients and their family members willing to participate in these clinical studies.

Dr. Page Pennell: 13:10 We learn a lot, a lot from animal studies. But there's that additional step that just cannot be reached without everyone's participation. This was a three side study at Brigham and Women's Hospital, Long Island Jewish Hospital, and NYU. The hypothesis, based upon the literature, was that women with epilepsy will have lower than expected pregnancy and birth rates, compared to healthy control women. We assess several different things. We had a partner who designed a diary with us that can be used on any smart phone. At the time, this was a little bit when it actually was an incentive to give someone an iPod. But it can be used as an app on iPod, for those of you who remember what an iPod is. But also any smart phone. There's a daily diary we had them fill out.

Dr. Page Pennell: 14:04 The epilepsy group, we filled out if they had a seizure, if they took their medications, if they missed a medication dose. There was also a daily reminder, also the medications were detailed in here. But we also had them track if they had menstrual flow, which was indicated by the pink flower. We also had them track the interlocking hearts, which some of you may jump to the conclusion that this was when they had sexual activity with their partner, when they had intercourse. The healthy control women also tracked the other non-epilepsy factors. Really, this was a good news study, that we were wrong. Based upon the prior literature, we thought that women with epilepsy would have lower conception and lower birth rates. But actually this is in months, so the women with epilepsy are in red, and this is in blue, that achieved pregnancy.

Dr. Page Pennell: 15:03 Really, the curves are essentially identical. Among our women, 60.7% achieved pregnancy, versus 60.2% in the controls, within 12 months. The median time to pregnancy was no different.

Then we also looked at sexual activity and ovulatory rates, and they were similar in women with epilepsy and healthy controls. The other thing that was really helpful is that to know is that there were no differences in miscarriage rates. So having epilepsy in and of itself does not increase the risk of miscarriage. Now, there are a couple things that are important. Our exclusion criteria was that someone could not be enrolled if they already had a diagnosis of infertility, or if they already had a diagnosis of polycystic ovarian syndrome.

Dr. Page Pennell: 15:53 We were not able to answer that part, that I mentioned before, that has been shown to occur more frequently in women who are on valproate with idiopathic generalized epilepsy. The other thing is, we did see a trend, if a woman was on an enzyme inducing medication, and I'll explain that in a minute, they were a little less likely to achieve pregnancy. I think that could account for some of the differences in the literature. Because in other parts of the world, or non-tertiary centers, women are more likely to be on these enzyme-inducing medications that could affect fertility. I hope to be able to adequately explain that in a little bit.

Dr. Page Pennell: 16:38 Moving on, and then I'll come back to that other issue, is what about the effects of the sex steroid hormones, estrogen and progesterone in and of themselves on the brain? Well progesterone is actually metabolized as well, to allopregnanolone, which binds at the GABA benzodiazepine receptor and causes inhibition. It has a similar action to benzodiazepines, such as Clonazepam or Lorazepam or Valium. In animal studies, it's really clear that estrogen promotes seizures, and promotes epileptogenesis. Whereas progesterone and its metabolite, allopregnanolone, protects against developing epilepsy and decreases seizures.

Dr. Page Pennell: 17:27 But as usual, it's always difficult to sort out all these things in patients and humans with epilepsy. But just to show you, so progesterone is metabolized to allopregnanolone, but also a few other compounds, which are also inhibitory. Whereas estrogen, estradiol over here is excitatory, and a few other hormones. Catamenial epilepsy. There are three patterns that have been described by Andrew Herzog, who's really the innovator in this whole area. You can actually find literature back in the 1800s at least, if not even before, that discusses the fact that women with epilepsy will report that their seizures can get worse around certain times of their menstrual period.

Dr. Page Pennell: 18:22 But it really wasn't until Andrew Herzog came along and really studied this in a very logical way that gave science to this idea.

And to not just dismiss it. For physicians to dismiss it, and that it is an important pattern. On the lower Y axis are the days of the period. Day one is the first day of menstrual bleeding, and a regular cycle would be 28 days to the next first day of bleeding. But because cycles can vary, we actually do a little bit to account for that, and we count backwards. But the most common pattern is C1, so catamenial epilepsy pattern one. This starts day three. Three days prior to the next period, through the first three days of the period. This is a time when estrogen is in blue, remains somewhat high. But progesterone drops very quickly. What we think it is, is the estrogen to progesterone ratio as well as how quickly it is changing that leads to increased seizures during this time period.

Dr. Page Pennell: 19:35 Now another pattern that's been discovered or described is C2 pattern, and this is around the mid-cycle, which is around ovulation. The estrogen increases while the progesterone lags behind. Again, you can see this disruption in the ratio, as well as it changing during that time. Then the third pattern is when there is not ovulation, as mentioned before, so an egg is not released. Then progesterone does not increase throughout the second half of the cycle. So therefore, there are increased seizures during anovulatory cycle from approximately day 10 all the way through to the next period. It makes it really difficult when tracking seizures and menstrual cycles, because if you don't know which cycles are anovulatory, it's hard to see this pattern, and it can interfere with looking at the other patterns.

Dr. Page Pennell: 20:31 We did, this is actually from the WEPOD study. We said, "Well what about the fact that we have all these women tracked with their menstrual cycles and their seizures every day, and they're not on hormones, I'm sorry, because they're trying to get pregnant." Sorry. Prior studies really had talked about women with temporal lobe epilepsy whose seizures were not controlled, and that one third of them have a catamenial pattern. We said, "Well why don't we take the women who are trying to get pregnant, because they have all types of different seizures." They have generalized seizures, they have focal seizures for other regions of the brain, et cetera. And look and see what the pattern is.

Dr. Page Pennell: 21:12 What was interesting is we saw the same thing that almost one third had a C1 pattern, which is the most common. But a few others also had a C2 pattern, or C3 pattern. Even when you take a less pure population of women with epilepsy with a variety of seizure types and seizure control, we still see a catamenial pattern, in approximately one-third to one-half of women with epilepsy.

Dr. Page Pennell: 21:44 This kind of brings up, can we use different therapies? And should we use them differently at various life stages? There are descriptions for cyclic and continuous treatments for catamenial epilepsy. The only study that was really a what is considered a level one evidence, was designed by Andrew Herzog, and this was funded by the NIH, and it was a randomized double-blind placebo-controlled phase three multi-center clinical trial. For those of you who may have looked, when new medications are coming out, what the evidence is for why do they get FDA approval? This is a gold standard. So someone would get the progesterone, and then another patient will get placebo, but they don't know which they're getting. The way the study was done is we gave, there are several centers, and I was involved in it, and progesterone oral lozenges were given three times a day, starting on day 14 of the menstrual cycle.

Dr. Page Pennell: 22:49 Then it was tapered on day 26 to 27, and tapered a little more on day 28 and then stopped. The women participating in it had three baseline months of seizure diary, and then three treatment menstrual cycles, where they received this treatment. Overall, there's no difference in responder rates. There's really no difference between the two groups. Except if women had a very strong C1 pattern, then they actually did respond to the progesterone. By C1 level, I mean, say if a woman has, let's say average daily seizure frequency is one. One a day. But then during the C1 pattern, which is three days prior to menstrual bleeding through the first three days of menstrual bleeding, she has three seizures each of those days, then her C1 level, she's going to have three times more seizures during C1.

Dr. Page Pennell: 23:54 Once you reach three, there was a big difference and the woman with that pattern had a very good response to progesterone compared to the placebo down here. Now, what I'll do is it a woman thinks she may have a catamenial pattern, I'll ask her to keep a calendar. If she meets this criteria of three or more, then we will often try progesterone lozenges first. This is just a secondary analysis that showed that the women who had this pattern actually had seizure frequency reduction, in relationship to their allopregnanolone levels. That's that metabolite that I mentioned that has a direct effect on inhibition in the brain. From that, Cynthia Harden and I wrote a review in Lancet Neurology. We came up with the algorithm for treatment of catamenial epilepsy.

Dr. Page Pennell: 24:50 If C1 level is greater than three, try the progesterone lozenges first. But if the C1 level was less than three, then another strategy that is in the literature is to use Clobazam, the trade name is Onfi. 20 to 30 milligrams per day during the 10 days of

increased seizure frequency, starting a little bit before and then tapering after. I hadn't had as much luck with this because of some withdrawal effect of seizure worsening. I do tend to instead use Clobazam as a baseline medication throughout the entire cycle. Then I increase the dose a little bit during that time. Other things that aren't in the literature, but not, again, studied as clearly as progesterone has been acetazolamide, also known as Diamox. I personally have not had good luck with this, but it is in the literature.

Dr. Page Pennell: 25:45 Obviously, some people respond. In fact, one of my recent patients who may be on ... We decided to stop the acetazolamide and her seizures got much worse. So clearly in some people it does make a difference. That begins day minus seven, until day one, first day of the next menstrual bleeding. Another thing actually we use pretty often is with a gynecologist I work with, where we prescribe continuous oral contraceptive pills without a placebo phase, and just give it continuously. Or Nexplanon is a progestin-only implant. So you take out the cycling of the hormones, and it can help seizure frequency.

Dr. Page Pennell: 26:29 Other strategies are to increase daily dose of some medications around the days of seizure worsening, such as if someone's on Levetiracetam they can tolerate it. But there's a lot of medications you can't increase without getting some side effects. Then kind of similar is medroxyprogesterone acetate, also known as Depo Provera, which again takes out the cycling of the hormones and can be helpful. But it does have some risk of osteoporosis. That kind of moves into the contraception and maybe explaining some of the other interactions we've discussed. I've mentioned before that there was what we call enzyme-inducing anti-epileptic drugs.

Dr. Page Pennell: 27:11 There's actually studies in men that show if a man's not a strong inducer, his hormones will be lower. Such as his androgens, his testosterone, and he will have lower sexual function on survey scores. It hasn't been shown as clearly in women, but it just hasn't been studied as clearly in women. Therefore, it's probably a similar effect. There are concerns about decreased libido and sexual function with some of the strong inducers. And if you remember, when we were discussing fertility, there are studies that suggest lower fertility with some of these medications. But those are especially, such as a study from India, where they were used more often. But in our fertility study, most women were not on inducers.

Dr. Page Pennell: 28:02 The strong inducers include are, "old medicines," phenobarbital, phenytoin, carbamazepine, primidone. But still, it's not just old

medicines. Oxcarbazepine, which is second generation of perampanel, it's a third generation AED, and causes strong induction of the hormones, meaning that the hormones are much lower if you're on these medications. I was just talking about androgynous hormones, so hormones in the person that can affect fertility, et cetera. It has the same effects if a woman's on a hormonal contraceptive. So the chance of an unplanned pregnancy is very high with these medications. Then there's the weak inducers, which are sort of in the middle. You can see a lot of relatively new medicines in this group as well. These medications don't interact or cause lowering of hormones, so it's not a concern with these.

Dr. Page Pennell: 29:02 Now, to make it even more complicated, is hormones can then affect the levels of some of our medications. The best well-known one is lamotrigine. So if a woman's on a contraceptive pill that includes estrogen or a vaginal ring that includes estrogen, her lamotrigine concentrations are here in the dark will be able half of what it would be if she were not on the estrogen. This is a particularly important factory during pregnancy. But if there's not an adjustment in dose, sometimes it can result in seizure worsening, once they go on the hormone or once they become pregnant. Or if they come off the hormone, then they can get some side effects of the medication, another thing to keep in mind.

Dr. Page Pennell: 29:51 In general, for contraception, because it's so important to have planned pregnancy, we do use a continuous combined oral contraceptives quite a bit, or the implant of the progesterone which can both help by eliminating sex hormone cycling. Another possible option or IUDs, and even though the Morena and Skyla have progestin in them, they only act locally in the uterus and they don't really get substantial levels into the bloodstream to be of any concern. Also it is actually a progestin. That's a great option. But again, it doesn't help with catamenial epilepsy because it has no effect on the cycling of the hormones from a woman's own ovaries. There was just a nice study by Anne Davis and Alison Pact that looked at insertion of Morena, and really showed how safe it was, with no effect on seizure frequency and no increase unplanned pregnancies.

Dr. Page Pennell: 30:51 Okay. So moving on to perimenopause and menopause, during the years, fertile years, we saw the individual cycles of estrogen and progesterone. But overall, the levels of estrogen and progesterone tend to be high. Then during perimenopause, so when the menopause transition begins, overall the progesterone levels are lower, while the estrogen levels are high, and then as they're going through the end of the

menopause cycle, the estrogen levels fluctuate very widely. This is probably accounts for some of the other known effects of perimenopause/menopause transition, such as hot flashes, irritability, et cetera. But you can imagine what this can do to seizures, right? Because estrogen is excitatory, and progesterone is inhibitory.

Dr. Page Pennell: 31:43 Now after menopause is reached, which is one year after the last menstrual period, then everything flattens out during that time and remains stable. We don't have great studies. There's a lot of reasons, I could go into why it's hard to study this. But we do have some suggestion that during perimenopause, that actually seizures can get worse. The main evidence for this really came from a survey by Cynthia Harden, and women reported, two thirds of them said that they had an increase in seizures during perimenopause. If they had a history of a catamenial pattern, they were more likely to have seizure worsening. But the good news is, after menopause was complete, they were more likely to have seizure improvement. In this study survey, she also found a report that a hormone replacement therapy was associated with an increase in seizures.

Dr. Page Pennell: 32:46 So she designed a study, as part of this study as well. It was NIH funded, but it got pulled early because of the information that came out about the risks of hormone replacement therapy. Prior to that, hormone replacement therapy was a very commonly used and almost all women going through perimenopause and post-menopausal. Anyway, the bottom line I just want to say is that compared to placebo, when hormone replacement therapy, which is a combination of a progesterone and an estrogen, were given, the seizure percentage went up. Focal seizures, any seizure types, and most severe seizure types. Even though the study was stopped early, we actually showed evidence that hormone replacement therapy in the traditional, the trade name was Prempro, can actually increase seizures, so it's still a consideration.

Dr. Page Pennell: 33:40 Because of course, hormone replacement therapy is still used when indicated for other reasons. The idea is that first of all, acknowledging these patterns are very important. And that a third of women with epilepsy are hormone sensitive. By identifying them we can figure out additional strategies to help with seizure control. I do want to say, I've been doing this a long time and it doesn't replace the other medications unfortunately. It's not as though we can just treat the hormone cycling and get rid of all the anti-epileptic drugs. But it can definitely provide some improvement in seizure control.

Dr. Page Pennell:	34:25	But as we recognize this, we can also think about developing other medications that can be used across other ages and genders who have the beneficial effect on the brain, but without some of the reproductive effects. There are some medications in development right now that meet those standards. I also think it's very important to acknowledge a pattern and to be reassuring to patients. I think it was common for healthcare providers to sort of dismiss it. I do think part of that reason is because there wasn't a way to treat it differently, at the time. But now, as we're starting to become more sophisticated about this, it is important to pay attention to these patterns in each individual person.
Dr. Page Pennell:	35:09	As we gain our knowledge and have sex-specific basic science and clinical research can lead to enhanced therapeutic options for the treatment of epilepsy and its comorbidities. With that, I'll turn it back over to Dr. Lubbers.
Dr. Laura Lubbers:	35:28	Great. Thank you so much, Page. That was really informative. And I think already addressed some of the questions that have come up from our viewers. But let's go ahead and dig into some of the questions that came up in advance. Here's one regrading a rare epilepsy. This person has noted clustering. The question is about PCH 19, and the person has noted clustering with menstrual period being a trigger for seizures. What's the best treatment for stopping the period to keep the hormones from triggering the seizures in somebody like this?
Dr. Page Pennell:	36:07	I actually had a slide about that and took it out. That is a very specific syndrome that is predominantly in females, and is very much related to this topic. There are some treatments that are currently in investigation and actually Dr. Lubbers, you might know more about the most recent, but really acts on that allopregnanolone basis. There's a synthetic allopregnanolone called Ganaxolone. So there was a treatment trial specifically for this. Then also allopregnanolone, it's only in infusion is a problem. But that's being used in post-partum depression, so that hopefully will also get to the point that it can be used directly and developed as not just an infusion. But do you know the latest on the trial results?
Dr. Laura Lubbers:	37:09	That's a great question. I know that it's still under study for some specific rare diseases, including tuberous sclerosis. I don't think the results have been reported yet, but that's a great thing to pay attention to, as those trials are progressing, and thinking about it in the context of not just general seizure control, but seizure control in women. Great point. Here's a question for you. Are there any known interactions between hormone

changes and epilepsy devices, such as the vago-neural stimulator?

Dr. Page Pennell: 37:46 Yes. There's no known interactions between that. There have been not so much publications, but some investigators have looked to make sure that it has no effect on the reproductive axis hormones. Now in addition to VNS, of course we have RNS now. I guess technically, it's a good question. If it's in an area that's going to cause a change in firing to the hypothalamus maybe. But I don't know that any studies yet. That gives us another great idea to try to get funding, and just to make sure, maybe in those people who have it in an area that's likely to cause hormonal change to look at the effect. But nothing reported to my knowledge.

Dr. Laura Lubbers: 38:38 Okay, okay, great. Thank you. Question related to polycystic ovary syndrome. How does elevated testosterone in PCOS figure into the progesterone/estrogen balance? And particularly, the influence of Estradiol on seizure activity?

Dr. Page Pennell: 38:57 Yes. Right. So polycystic ovarian syndrome can potentially increase seizure frequency by first of all having more anovulatory cycles. Going back in the slides, I don't know if you remember, but a C3 pattern, when you have anovulation, you don't get the rise in progesterone, so you can have increased seizures because of that. Then as mentioned, it also causes hyper-androgynism, and testosterone levels. Back in the slide, I don't know if I can go back, there is a metabolite, of testosterone, DH, which is an androgen, DHEAS. Which can be excitatory. Those are two ways it could contribute potentially to increased seizures. DHEA sulfate is actually from, you can see here's the androgen and testosterone. Those don't directly have an effect on seizures. They do have an effect on the brain, but not on seizures that we know of.

Dr. Page Pennell: 40:09 But also, the androgen can maybe decrease the DHEA sulfate, which could increase seizures.

Dr. Laura Lubbers: 40:18 Okay. Does supplementing progesterone have an impact on the elevated testosterone?

Dr. Page Pennell: 40:25 Not that I know of.

Dr. Laura Lubbers: 40:28 Okay.

Dr. Page Pennell: 40:28 Supplementing progesterone, yes. Not that I know of. Yeah. Good question though.

Dr. Laura Lubbers:	40:35	Okay, yeah, indeed.
Dr. Page Pennell:	40:36	Yeah.
Dr. Laura Lubbers:	40:38	Why do you prescribe progesterone lozenges for the C1 group rather than birth control?
Dr. Page Pennell:	40:44	The lozenges that were used in the study are actually pretty high dose compared to the progesterone you would get in any of the birth control options. But more importantly, in the birth control options are synthetic progestins. They're not quite this progesterone. The synthetic progestins do not metabolize to allopregnanolone. You really need natural progesterone and it is not easily taken as a pill, and actually gotten into the blood system through GI absorption. There's two ways to give it, which is a lozenge, which it gets through the mucosa into the bloodstream. Or as an actually vaginal suppository. There is a micronized progesterone that can be taken as something you swallow, so that is another option.
Dr. Laura Lubbers:	41:47	Okay. All right. Here's a question about the post-menopausal period. Can medications, and I think you addressed this, but it's good to reiterate. Can medication become less effective post-menopause?
Dr. Page Pennell:	42:01	So post-menopause, often seizures get better, and the medications are still effective. It is possible to have some seizure worsening during the menopause transition. It can actually take quite a while. It can be anywhere from two years to seven years. I have worked with our gynecology specialists on suppressing that erratic hormone phase through other hormones to try to stabilize that. In rare instances, we've even gone to suppression of the hormone axis with things that are such as used in in vitro fertilization techniques to completely shut down the hypothalamus, pituitary, ovarian axis. But again, I only do that in concert with reproductive endocrinology specialists.
Dr. Laura Lubbers:	43:00	Okay. We have a listener who makes the point that there's still too many doctors who dismiss the issue in women. And I agree. Do you have any advice? Actually now we have these transcripts, and people can take transcripts of these recordings to their doctor. But what would you advise somebody who's faced with a situation like that?
Dr. Page Pennell:	43:24	Yeah. It's unfortunate. I certainly got into women's health issues and epilepsy because of a lot of the stigma that was there, that

is actually often present in women's health across all disorders, but especially epilepsy. We just didn't have information, scientific data to be able to discuss it and that also pertains to a lot about pregnancy issues. I think the best way is still to bring information to them with some of the studies that show that a third of women with epilepsy have this pattern, and there are considerations as far as different strategies that could be added on to the primary strategy for controlling seizures that can be a benefit.

Dr. Page Pennell: 44:19 If the doctor or PA or nurse practitioner doesn't listen then, then find a new doctor. I know it's not that easy. There's a lot of areas in the country there are not enough neurologists, never mind epileptologists. But certainly, I've had patients move to other areas of the country where they didn't have the same resources, and that they brought the information to the doctor and it was really actually very, very effective.

Dr. Laura Lubbers: 44:47 Okay, great, great. Thank you. Does Epidiolex, or CBD, have positive or negative effects on catamenial seizures? Or do we know?

Dr. Page Pennell: 45:01 I don't know. It's also a good question. I do know that Epidiolex has a lot of interactions. The first question I would have is how does it affect these pathways? I haven't seen anything with it yet. But obviously it's still not as commonly used in women of reproductive age as some of the other populations. So I don't have any information yet.

Dr. Laura Lubbers: 45:33 Okay, okay, thank you. Here's a specific question about a particular medication, and I'm hoping I'm going to speak to it correctly. If you are thinking about getting pregnant, what is the safest way to get off of a medication? For example, Trokendi RX, or XR, beforehand.

Dr. Page Pennell: 45:53 Yeah. So first of all, the question is really, really important. We know that 50% of pregnancies are unplanned, and then we have that extra in the United States, and then we have that extra problem we talked about, about interactions and causing lower efficacy of some birth control options. The best thing to do is yeah, if you can plan the pregnancy, and to speak with your neurologist hopefully about how to get onto the safest medication regimens. We have several medications which are very safe during pregnancy. It really should be the exception to stay on a medicine that's not as safe, because you've already tried the other medications and they don't work for your epilepsy.

Dr. Page Pennell:	46:46	Topiramate is one that is in the middle, where it does have some increased risk, especially for small progestational aged births, or low birth weight, and a slightly increased risk of cleft lip and cleft palette. But it's also not one of the most dangerous ones. If the other medications were tried, and they weren't effective, certainly it would be possible to move ahead with a pregnancy on it. But as far as how to switch over, that is so individualized according to seizure types, seizure frequency, background, what's been tried, side effects, so many things that it's not one size fits all, but hopefully it's a good partnership with your neurologist to get to that point.
Dr. Laura Lubbers:	47:30	Great. It's great to know that those steps, that it's a discussion that needs to be had, and you work together to do that.
Dr. Page Pennell:	47:37	Right.
Dr. Laura Lubbers:	47:37	Great. Have you heard of seizures destabilizing in males as it they go through puberty? Does aromatization of testosterone to estrogen play any role? Great question.
Dr. Page Pennell:	47:49	Yeah. I don't know, obviously. Because I'm taking too long to think about it. But I did mention how some seizures begin around puberty. I should've mentioned that there are certain epilepsy types that the seizures get better as someone moves through puberty, or even goes away. The obvious is childhood absence epilepsy, or benign rolandic epilepsy. But I don't know, yeah, if it's been studied beyond that. Actually at the end, we were talking about the menopause transition and how we need more studies on it. But likewise, the pubertal transition is another thing that definitely is understudied.
Dr. Laura Lubbers:	48:40	Yeah. What a great model to study as well, because we understand those transitions.
Dr. Page Pennell:	48:47	Right.
Dr. Laura Lubbers:	48:49	As a woman with epilepsy who's hoping to become pregnant, how can I find out about research studies I might be able to qualify for when I do become pregnant?
Dr. Page Pennell:	48:59	Yeah. There's a few ways. There's our pregnancy registries, which have provided such incredibly helpful information to know a lot more about the risk versus benefits of many different medications, medication combinations. In North America, there's the North American AED pregnancy registry, which can be found pretty easily through the website. I

encourage everyone to enroll in. It's only a few phone calls, it doesn't take much time. Likewise, there's international ones such as EURAP. Then for other studies that are very active, you can look under ClinicalTrials.gov has a listing and search by epilepsy, and that gives information about trials that are ongoing. We have a very large study going on across the country, in case anyone also participate in that. It's called MONEAD, Maternal Outcomes and Neurodevelopmental Effects of Anti-Epileptic Drugs. It's 20 sites across the country.

Dr. Page Pennell: 50:06 But we are fortunately in the latter stages of it, because so many people volunteered time, and for their families. We're not enrolling new families at this time, but believe me, we are always looking for funding to continue the quest to get all the answers. Likewise, there could be something new that's happening at that time. You could also check with your local Epilepsy Foundation Chapter. But again, if there's any study that involves humans, we have to actually register on ClinicalTrials.gov. That's always a good place to look. Then you might have something through CURE Epilepsy, Dr. Lubbers, as a resource?

Dr. Laura Lubbers: 50:49 We would also guide people to ClinicalTrials.gov. It's the biggest resource, most accessible, for the most current studies. How frequent do women with epilepsy develop preeclampsia? Will preeclampsia worsen the woman's epilepsy?

Dr. Page Pennell: 51:08 Yeah. So I know it's frustrating to get mixed messages. But there were some studies that suggested that preeclampsia was more likely to occur in women with epilepsy, and those were studies that looked at hospital records, which is coding. They're not as pure. Because whatever is coded for insurance reasons. It's not very specific. In the MONEAD study that I just mentioned, we actually had a primary aim of looking at obstetric complications, and there were actually no increased rates of preeclampsia, eclampsia, in women with epilepsy versus the general population.

Dr. Page Pennell: 51:50 But obviously, women with epilepsy could still develop preeclampsia. It doesn't seem to make her underlying seizures worse. But of course, if she goes on to eclampsia, she can develop seizures because of the other vascular effects of eclampsia. It doesn't seem to be an increased risk in women with epilepsy.

Dr. Laura Lubbers: 52:12 Great, thank you. Can repeat seizures lead to loss of libido in women of childbearing age?

Dr. Page Pennell:	52:21	That is a great question. We think that's possible, as we mentioned, the medications can cause decreased libido, depression can, and the treatments for depression can. A lot of the medications that are used for depression can also cause decreased libido. It's multifactorial. We did want to look at this really specifically in WEPOD, that study I mentioned where we had women track their sexual intercourse according to their menstrual cycle and their medications, but we had a collaborator who's an OB-GYN, and she was so helpful to remind us of these basic things that we don't think about as neurologists, which is that once a person is trying to get pregnant, sexual intercourse has very little to do with libido. Its primary goal is very different. She did not feel that we could use our diary data to address libido whatsoever.
Dr. Page Pennell:	53:22	There is some nice work by Martha Morell to go back and look at, that does show some interactions with types of epilepsy and also medications. But untangling all those things, such as frequency of seizures, isn't completely clear. But I think it probably is linked to frequency of seizures to some degree.
Dr. Laura Lubbers:	53:47	Thank you. This question is a little different in a way. This person mentions the start of seizures that included tonic-clonic and absence seizures starting around 12 years of age. Depakote and Onfi has been offered as the best seizure control so far, and it seems like growth has slowed drastically. This brings in another hormonal paradigm, with a delay in menarche at about 16, at almost 16. Can medications or the seizures be responsible? I think particularly around the growth issue? And what would be good treatments for people to keep in mind?
Dr. Page Pennell:	54:29	Around the growth, I'm not sure. First of all, I should say I'm an adult epileptologist. That's where a lot of my hesitation is. Because although I'll see someone who's 16 because they have a hormonal problem or a concern, hormonal concern, or they become pregnant, I don't practice during that earlier phase. Now, that valproate in particular has actually also been shown to cause lower androgens and lower sperm count in men with epilepsy. She said it could be affecting other hormones. I'm going to turn it back to Dr. Lubbers. Do you know the answer?
Dr. Laura Lubbers:	55:13	I don't. Actually, I don't know in this context about growth and epilepsy. Yeah. Yeah. Good question.
Dr. Page Pennell:	55:19	Sorry. You'll have to bring on a pediatric epileptologist next time.

Dr. Laura Lubbers:	55:24	Yes. Okay. Okay. Very good. One last question, is there an over the counter way to check progesterone and estrogen levels for somebody who might want to track what's happening with their cycles?
Dr. Page Pennell:	55:42	Not over the counter for progesterone. But what you can do, is very effective, is do LH test kits. Luteinizing hormone is the hormone that's released right before ovulation, and it causes the egg to be released. Then after the egg is released, then the corpus luteum stays behind and that releases progesterone. You can use LH test kits. They're most commonly used for fertility, when someone's trying to get pregnant, to see if they're ovulating. You can actually get batches of them cheaper, such as through Amazon or some other source, if you are going to be doing it on a regular basis. It'll tell you where to being. Usually around day 10, you do a urine sample every day. Then it'll tell you if you're having the LH surge. It is very accurate, as to whether a person's ovulating or not.
Dr. Page Pennell:	56:35	Although it won't give you the progesterone level if you're not ovulating, it means the progesterone level's low. The other thing we do in research settings are check day 21 progesterone level, because if they're ovulating, that's where the progesterone should be at the level we want. Then sometimes I'll do it before starting the progesterone lozenge treatment. Then after I start progesterone lozenges, I check it again, and I want to make sure it gets above 20 nanograms per milliliter. If you're going to check it, check it at day 21. Or if you want to see it over several cycles, if there's ovulation occurring, then you can use the LH test kits.
Dr. Laura Lubbers:	57:13	Great. Thank you. Thank you again for a terrific presentation. It was very informative. I want to also thank our audience for all of the questions. I know we still have very many, many open questions, and we will see if we can synthesize some answers with the help of Dr. Pennell. If you have additional questions about this topic, would like to suggest a future webinar topic, or wish to learn anything more about the CURE Epilepsy research programs or future webinars, please visit our website or email us at Research@CureEpilepsy.org. Also be sure to register for our next webinar on April 13th that will spotlight the mental and social health effects that epilepsy has on siblings of children with severe epilepsy.
Dr. Laura Lubbers:	58:01	Again, thank you very much for your time Dr. Pennell, and to our audience, please stay safe. Enjoy your day.