Welcome to the Cutting Edge Health Podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

[00:00:00] Jane Rogers: Welcome to the *Cutting Edge Health: Preventing Cognitive Decline* podcast. I'm Jane Rogers. We've all heard that it's very important for women to pay attention to factors that can lead to cognitive decline because women get Alzheimer's at a way higher rate than men, two and a half times the rate that men get Alzheimer's. I ran into Dr. Felice Gersh. She is an OB/GYN and also an integrative medical doctor; she does functional medicine, and she knows all about hormones. Hormones are so important for a woman, whether you're perimenopausal, whether you're menopausal and have already gone through that phase in your life. Hormones are important to protect your brain, and she explains it so well in this interview. I hope you enjoy it. Felice, thank you for joining us today.

[00:00:48] Dr. Felice Gersh: It's my pleasure. I'm so happy we could do this. We matched our times. We've worked hard on this, haven't we? You're very busy. It's wonderful to get together. I'm so happy we did.

[00:00:58] Jane: Thank you. Me, too.

[00:00:58] Dr. Gersh: We're doing it.

[00:00:59] Jane: Thank you. Your expertise is exciting to me. OB/GYN certification and also integrative medicine, so you really understand how a woman operates, and women get Alzheimer's at such a higher rate, and this is what this audience, I think, is most concerned about: how to protect our minds from cognitive decline.

[00:01:17] Dr. Gersh: Well, it happens to be, when they do surveys, the number one dreaded fear. That is true and not without reason. Women have significantly higher rates of developing Alzheimer's disease and there are other forms of dementia as well that occur in women. Women develop Alzheimer's at least two and a half times more frequently than do men. That doesn't really get enough traction out there, that this is a huge problem. People always focus on women living a few years longer. Well, who the heck cares if you're living with dementia?

[00:01:52] Jane: Yes, you're exactly right. As an OB/GYN, there are many components to what brings cognitive decline to women. Do you feel one of the main drivers would be hormones and menopause?

[00:02:05] Dr. Gersh: It absolutely is. This is why it is so frustrating to me when there was, for example, just this past week, a new series of articles in the very prestigious medical journal, *Lancet*, that said, stop creating this rumor, this craziness that you should

consider menopause a medical problem and you're, like, over-dramatizing it. That is ridiculous. They said it's not really a hormone deficiency. Of course, it is a hormone deficiency and we should treat it as such. Instead, in this prestigious journal, they're talking about you should treat it with sometimes other pharmaceuticals for symptoms. Otherwise, you can do mindfulness meditation, you can do more exercise, you can work on sleep hygiene.

Now, don't get me wrong, 100% for lifestyle medicine, mind-body medicine, exercise, fitness, sleep, stress reduction, working on lowering exposures to the environmental pollution, the toxicants in our environment, 100%, I'm for all those things. They are necessary, but they are not sufficient. If you had your thyroid gland removed, no one would suggest, hey, it's okay, why don't you just meditate more? No, they would give you thyroid hormone. It would seem so absurd, and we could go through every single endocrine deficiency state. How about type-1 diabetes? You can't do sleep hygiene or exercise your way out of not having insulin. You have to have it to survive.

Well, you can survive to a reasonable degree without the ovarian hormonal production of estradiol and progesterone because there are ways that you can get it, but not in sufficient amounts. You live in a body that is just suboptimal for the rest of your life, which for so many women now is literally half their lives because of this amazing longevity that we have now in our modern society which has never existed in the history of humanity. Women literally can spend half their lives as menopausal beings and not in the best of shape.

Menopause never heralds the beginning of a better state of health. Menopause doesn't create health. You have to work hard to be healthy and be menopausal. We need to just recognize what it is. It's a hormonal deficiency state, and we need to give hormones, but we need to do all the other things, too.

[00:04:38] Jane: Like with any deficiency state. If you are low on magnesium or low on vitamin D, you're not going to fare very well.

[00:04:44] Dr. Gersh: That's right. That's another great analogy. I'm going to steal that one, too, because everybody knows if you're deficient in a vitamin, you can't meditate your way out of it. It's like they're actually abusing our beautiful, holistic approaches by substituting them for the needed hormones or nutrients, like the micronutrients, the macronutrients. If you're starving, meditation is going to get you just so far. You have to have food, and you have to have hormones. It's so basic. It's like the biggest duh. Duh, you don't have the hormone, you get the hormone and then you do everything else.

When you look at the neurological system, well, first, if we go back, because I delivered in my heyday of doing obstetrics, which I did for 25 years in my medical practice and delivered thousands of babies, it became so apparent to me. It's like such a strange thing

that this isn't really universally apparent, that the prime directive of the female body is reproduction. Whether you want to have babies, don't want to have babies, that is not the point. The point is that from an evolutionary standpoint, our bodies evolved as females to be successful with making babies, nursing them, raising them, and doing this process a few times over to maintain the population of humans.

To that end, the hormones that are ovarian--we'll put testosterone on the back burner for the moment--but we'll say estradiol, the estrogen of the ovaries, and progesterone. In order for that to be successful, for there to be successful reproduction, you have to have these hormones, not just to make menstrual cycles, to ovulate, but to support every organ system because to be successful as a reproductive creature, you need a really healthy neurological system, you need a healthy musculoskeletal system, cardiovascular system, skin, genital, urinary, you go through everything, every system in the body.

They all have to be working in the same time zone, they all have to be working in synchrony, and they all have to be working optimally because ultimately, pregnancy, which is apparent to anyone in the obstetrical world, is now recognized, even widespread, as the ultimate stress test of the female body. In order to be successful, which is not happening in great numbers now, we're having so many pregnancy-related complications, you need to have all those organ systems optimally healthy before you even conceive.

We now know, for example, that women who have problems with pregnancy, whether it's gestational diabetes, gestational hypertension, preeclampsia, abruption, preterm labor, you name it, any kind of complication, a baby too big, a baby too little, any of those complications, they are portending of future problems when a woman goes through that menopausal transition. Women who have emotional issues earlier in life, for example, postpartum depression or PMS or any kind of anxiety or depressive kind of state, when they go through the menopausal transition, they are four times at elevated risk of developing one of those emotional problems, whether it's depression, anxiety, and so on, once they go through and are in the process of going through the menopausal transition.

We know that, for example, Alzheimer's disease is not just a cognitive decline, it's also a condition of emotional instability. Emotions and cognition are completely intertwined. We need to be very aware of, we'll say, the fortune telling that we can do with good scientific foundation, that if you have problems with fertility, for example, even women who have irregular menstrual cycles, infertility, as well as pregnancy complications, they are a much higher risk group for having problems as they transition into menopause. The whole idea when you practice integrative and functional medicine is to have an expanded therapeutic toolbox, but also to identify people who have higher risk of having certain adverse things happen to them in life, so you can be even more proactive.

I've renamed them from sex hormones to life hormones. When you lose them, you lose, we'll say, the foundation for optimizing health in every organ system, and the brain is a huge one. Not just the brain as a neurological structure, but the autonomic nervous system, which doesn't get its day in the sun either. The autonomic nervous system controls all the things in the body that we don't think about, like our blood pressure, our pulse, sweating, peristalsis or motility of the gut, how our digestive enzymes get secreted, and when the gallbladder contracts, and all those different things. That is heavily related as well to our cognitive and emotional state, which doesn't really get recognized.

The same neurotransmitter, acetylcholine, that works in the brain to cement memories in the autonomic nervous system, is the neurotransmitter of the parasympathetic part of the autonomic nervous system. That's like what should be the baseline. It's like you're calm, you're digesting, your heart isn't beating too fast, everything is good, like homeostasis, calm, good. That same neurotransmitter, acetylcholine, is the prime neurotransmitter for the parasympathetic nervous system. The big nerve from that, which is like a big finger of the brain, is called the vagus nerve, which many people may have heard of, but they don't know what the heck it is.

We call it vagal tone when you have adequate output and function of this big finger of the brain that they call the vagus nerve that has little branches of nerves that go everywhere that maintain everything in a calm state. That's why there's this incredible interconnection between emotions and gut health and heart rate and all these things like the stress effect and how it affects all these different systems. That's all under the control of estrogen, the estradiol form of estrogen that is made in the ovaries. After menopause, you have so many dysregulations involving the neurological system that don't get recognized even among neurologists.

[00:11:48] Jane: There are so many questions I want to ask you as an OB/GYN with years of experience. When it comes to hormone replacement, is it ever too late to start? What if I went through menopause years ago and I haven't been doing estrogen and now I'm 65, 70, 75? Can I start now?

[00:12:04] Dr. Gersh: This is, I call it, one of the key questions that is so critical because now, although it's not really looked at from any point of view other than symptom control, I have to be realistic in our conventional medical world, it's still very sad that they only look at treating menopausal symptoms. Those would be classically like night sweats, hot flashes. Sometimes they'll throw in other sleep disturbances that are separate, or palpitations or joint pain, but usually not. Usually, they just say night sweats and hot flashes and leave it at that. It's all about symptom control, and they're not even thinking about all the covert, the not obvious things that are happening in the body with the loss of these vital life hormones.

When it becomes obvious that bad things are happening, even in women who may have used other products, maybe pharmaceuticals, or maybe they just toughed it out, and now, like you said, they weren't on hormones and now they're, say, in their 60s or even in their 70s or could be older, but they went through the whole menopausal transition. Maybe they were briefly on hormones or typically not at all, but now it's been years and now they're starting to see what was covert, was hidden. Now it's becoming more obvious.

For example, you don't feel changes in your arteries that lead to vascular damage and hypertension. By age 65, it's amazing, 75% of women at age 65 will have hypertension, high blood pressure. That is not an early stage of vascular disease. It was happening silently all those years preceding age 65. We'll say if a woman went through menopause at average age 50 to 51, so we're talking like about 15 years with a hormone deficiency state in her body, now she suddenly has high blood pressure, or maybe she is now recognizing that she is having some real cognitive decline.

Maybe she's on drugs for sleep, maybe she's on drugs for mood, maybe she's having a lot of digestive problems. After menopause, women surpass men in the incidence of gastroesophageal reflux, because, once again, the autonomic nervous system which controls gut motility is not working properly and so things aren't working right and they get more reflux and a lot of things are starting to happen. She may have had a fracture or has now had one of those DEXA scans done and told, oh my gosh, you have osteoporosis. In fact, the conventional medical world doesn't even recommend doing a DEXA scan until you hit 65.

[00:14:58] Jane: It's crazy.

[00:14:59] Dr. Gersh: She gets on Medicare, she's now 65 because they're not about early detection. Now she goes in, her internist orders a DEXA scan, you're now 65, you're on Medicare, oh look at that, you have osteoporosis. Now we want to put you on a bisphosphonate or we want to put you on the drug Prolia, we want to put you on a drug and there's no long-term strategy because these drugs have a lot of problems over the long haul.

Some of them, like the bisphosphonates, you can't even be on for more than a very, very few years because it basically creates a body of dead bone. It's not too useful in the long run because it blocks bone turnover. It just makes you keep your dead bone instead of replacing it with healthy bone. In the short run, if you have a very short life expectancy of five years, it may be useful, but that's not what we're talking about. We're not having five-year life expectancies here.

Now you have this large array of women who are told, you have atherosclerosis, you have hypertension, you have osteoporosis. Maybe they have now incontinence much more and now they're wearing adult diapers and they're looking at surgery, they're having prolapse,

having all these things that are associated with aging. They're having glaucoma, macular degeneration, and they say, can the hormones help me?

Here's the reality of it. I believe it's better by so much to start early because that's being proactive, but we are where we are in our life journey. I believe, but there's a lot of things I cannot prove, so I have to preface it with that. I believe that starting hormones, now we're talking bio-identical hormones, estradiol, and I just want to make sure people know estrogen is not a hormone. That word is misused so much. It's a family of hormones. It comes in an adult woman, three types, and they have a number like one, two, three, and a letter, which is always a big E for estrogen, and a word.

It's a little bit like the B vitamins. B vitamins have the letter B for B vitamin, a number, like one, two, three, up to like, 12, and then they have a name. Like B1 is thiamine. B12 is cobalamin. Each one has a name, a number. Estrogen has E1, E2, E3. The estrogen that the ovaries make is called E2, estradiol. The full name would be 17 beta-estradiol. We just say estradiol, or, we can say E2. They're different. Their differences are significant because they bind to receptors.

Hormones go together like a lock and a key. It's like the best analogy, even though it's not really exact because receptors, unlike a lock, can actually shapeshift. They can be more open, more closed where a lock is a lock. Receptors can actually become more variable, like a mouth can open, close, and be different shapes. Each type of estrogen has different effects on the different receptors. They're not synonymous. They're not identical, just like B vitamins are not the same. If you had a B12 deficiency, you wouldn't solve the problem by giving B1. We just have to think about that they're not the same, even though they're cousins.

When you want to give hormone replacement, you have to give the hormones that the ovaries made during the reproductive years with the goal, although this is not really achievable, but it's our mission to try to get reasonably close, at least somewhat close, to give hormones that are somewhat similar to the amounts and rhythms of hormones of women when they are the healthiest, which we'll say in their 20s. Okay, so we don't want to give ridiculously low amounts or ridiculously high amounts. We don't want to give them in ways that the human body never had them. We're just not trying to be that creative.

We try to be, as a society, creative with food, like with food processing, that did not work out too well. Sometimes it's better to just let nature be itself. If we're going to trick nature into thinking we're young, we've got to give hormones the way we had them when we were young, and that is rhythms and levels somewhat similar. We can't replicate it exactly, but we can do better than what most people are getting when they're getting hormone therapy by far, because it has often nothing to do with what nature ever had in the female body at any time in life.

Here's the thing. When you are older and you already have issues with bone loss, osteoporosis, and vascular disease, tissue degradation, like osteoarthritis, your joints are damaged and tissues are falling down, like lack of support and so on, we can't resurrect everything to be like before. At the very least, I think, we can slow the progression of damage, okay? Maybe we can also do some reversal.

The sad thing is that because there is so little interest in this entire area of women's health, which is shocking when you think about it, we really don't have the data. We just, we don't have it. Here's what I do have, some limited data, which is why I support giving women at any age, and I want to go back over what is the conventional approach though, at any age with few exceptions. If someone has had breast cancer, that would be a moment to pause and think about, is this appropriate for this person. I'm not saying there are no exceptions, but we're saying in general, for the majority of women, no matter how old you are, you will still get benefit, even if it's not as good a benefit as it would have been had you started much earlier.

Now, what can I even base that on since we have so limited an amount of data? Well, the ELITE study, which was completed a few years ago, had two arms. In one arm, they used women who were close to menopause. In the other arm, they used women who were much further out from menopause and were older. The study used the wrong form of estrogen. It used a very small dose of oral estrogen, which is not the right way to give it because by the time it goes through the liver, gets metabolized, it goes into the bloodstream as the wrong form of estrogen, predominantly as E1 instead of our beloved E2, okay? Right there was a problem, the dosing and the modality of delivery. Even with that, what did they find? No harm. At least we have that. No harm happened to those women at all.

Now, what else do we have? We have this gigantic movement that's within the Menopause Society and all the different organizations, the American College of OB-GYN, to give women local estradiol in the vagina. It's like they're pushing it like crazy. I'm not against that, it's just not enough. Why are we treating one system, one tissue? Why are we not treating all the tissues? Here's the thing. You can take a woman who is out any number of years from menopause, any number, it doesn't matter, they have no restrictions, and they give it and they're recommending it so that women can have a sexual life, have better health in those tissues in terms of comfort, and it improves the bladder.

Think of it, the vagina is like the guardian of the bladder. Many women, after menopause, will develop chronic urinary tract infections, a lot of bladder infections. Not just that, they'll have all the symptoms that are so unpleasant, urgency, frequency, and incontinence, and all of these things. By giving women vaginal estrogen, it sort of permeates the local tissues down in that area. Guess what happens? They get better, they improve. Why would I think that after potentially decades of no hormones, you can give vaginal estrogen in a

variety of rings, creams, tablets, like all these different forms? It always, not like sometimes, if you give enough, you will always get improvement of those tissues, always.

Why would I think that only that one structure in the body, the vagina isn't even just one structure because it has connective tissue associated with the epithelial tissue. It's like a type of skin, but also then you have the bladder and you have better immune system in the area. Why would I think that only those tissues can benefit after years of, we'll say, lying dormant without any hormones?

Also, we have definitely good data that you can take estradiol, topical, put it on wrinkled skin, and in just two weeks, you'll see reduction of wrinkles. There's also quite a bit of data that you can give topical estrogen, and it doesn't matter how old the person is, it will improve wound healing. It will help wounds to heal because estradiol increases blood flow, new blood supply, new blood vessels, healing growth factors, new tissue formation, and so on.

We also have the Women's Health Initiative, that awful study that did so much harm because they used the wrong products, but in any case, they used older women, they used the wrong hormones, but even then, what did they show? Fewer fractures. In older women, when they gave estrogen, their bones were better off, and there was a reduction, these are quite significant numbers, in colon cancer. It was good for the colon.

We have now, to me, this is enough. I can't prove that it's going to reverse brain damage. We have, of course, Dale Bredesen, who is phenomenal in the world of Alzheimer's, and he is giving estradiol to the vast majority, with few exceptions that are necessary, of elderly women in his studies because he believes, and I'm so happy to call him a friend, that he believes that hormones are really beneficial to the brain. Of course, they are.

We have tons of science. We know what estradiol and progesterone do as neuroprotectants. They improve synapses, myelination. The progesterone and estrogen together, they each work in all these different ways, like progesterone helps to create myelin, and also neurogenesis and neuroprotection. Estradiol creates more synapses and neurogenesis and neuroprotection, and also creates what we call autophagy. That's regeneration of tissues.

[00:26:45] Jane: Which is huge, huge for your brain.

[00:26:46] Dr. Gersh: It supports mitochondrial function so that you have energy. You can't have a brain without energy and vascular health. Estradiol maintains the production of that vital gas called nitric oxide that maintains vascular health, so you don't get hypertension or leaky arteries, leaky blood-brain barrier. Estradiol maintains all of that because vascular dementia can be its own terrible thing, and interconnect, of course, with Alzheimer's. When you get bad vascular health, and you get the impaired blood-brain

barrier, then you get no protection from all the circulating environmental toxicants, heavy metals, pesticides, herbicides, and viruses.

Now we know, when you do autopsies on brains of people with Alzheimer's, it's amazing what they find in there, right? In terms of toxicants and viruses. You want to have a healthy immune system. That's the other thing. Estradiol maintains the functionality of the immune system. There are receptors on all of the immune cells. For estradiol and progesterone it's a very key player. It modulates the two of them, the endocannabinoid system, which is a lipid signaling system that's really key, as well as the other system that's involved with specialized pro-resolving mediators.

The endocannabinoid system is lipid signaling agents that are involved in multiple organs. There are tons of receptors for the endocannabinoid system in the brain. They work on many, many functions in the brain. They have a real dynamic relationship with estradiol and progesterone. The reproductive organs are phenomenally interesting. This other set of lipid signaling agents called the specialized pro-resolving mediators, which help to promote resolution of inflammation, they are heavily reliant on estradiol as well. It's because estradiol modulates the immune system so it turns on inflammation when we need it.

When should we turn on inflammation? If we're being invaded by a pathogen, like a virus or a bacteria or fungi, or if we have injured, damaged, or dying or dead cells, we want to activate the immune system because what they do is they put out like dissolving materials that dissolve the dead tissue or the pathogen, and then the gobblers that phagocytize, that gobble up these dead cells or pathogens and gets rid of them. We call them the DAMPs and the PAMPs, the damage and the pathogens. You want to have inflammation when you need it or else you will die, or you can't get rid of dead cells. That's part of the problem of aging is that we don't actually get rid of what they call senescent cells.

[00:29:52] Jane: The zombie cells.

[00:29:53] Dr. Gersh: The zombie cells, we don't get rid of them. They have misfolded proteins, they create inflammation, they can turn into cancer. Estradiol modulates the process of getting rid of those zombie cells, the senescent yucky cells, and turns on inflammation when we need it to fight off infections, to get rid of injured tissue, and then turns on the anti-inflammatory and pro-healing resolution phase that helps you to create new tissue, to heal, to dampen down the inflammation.

Because if you have an infection or a burn or an injury on your skin, first you have the inflammation to keep from getting infected, like from invading bacteria, and then you have to dissolve and get rid of the dead cells from that damage, the burn, and then you create new cells. We don't even think about it, right? How is it that we have a burn and it just

gets better? You can't even see it in most cases, right? It's all under the control of estradiol. It works with other hormones; they're all interconnected in this incredible web.

For example, thyroid. Thyroid glands have receptors for estrogen. If you don't have enough estrogen, your thyroid doesn't work properly. Of course that's heavily involved in metabolism, in weight, in appetite, in energy, in heart function, in brain function. If you don't have enough thyroid, you have depression, you have all kinds of problems. There's a complete interconnection with these hormones and estradiol is key in everything. You don't want to lose any of them. They're all vital hormones.

If I had created a pyramid, I would put estrogen at the top, but you need them all. We don't just say, ah, we don't need thyroid. Of course, we need thyroid, but you can't have proper functioning of thyroid without estrogen. When you lose your estrogen, for example, when your hormones go away from your ovaries, your microbiome, this is like the new frontier of medicine, is understanding the microbial life forms that live on us and in us. The biggest collection is called the gut microbiome. There are trillions of different microbes, thousands of different species. Estradiol actually is key. That's not the only hormone that's key, but that is, stress hormones like cortisol also changes.

We know now that every woman, when she transitions into menopause, the microbiome composition changes for the worse and it becomes what we call dysbiotic. That creates more impaired gut barrier function because you don't make the protective mucous coating and you get the famous leaky gut, and then the toxins and microbes in the gut leak into the body proper, creating an inflammatory response. That can also trigger antibodies against the bacteria and viruses coming in that can lead to more autoimmune diseases, particularly rheumatoid arthritis, which is much more prevalent in postmenopausal women. By far that's the greatest percentage of people who get that disease, which is not good.

Inflammation, the immune cells, become more reactive. They'll make more inflammation with a lower provocation after menopause when this toxic stuff comes in, we call them endotoxins, come into the body proper and create inflammation. That inflammation creates systemic inflammation and neuroinflammation, inflammation in your brain, and inflammation in the brain underlies deterioration of neurological functions in your brain.

The problem is so complex because you have changes in creation of energy, changes in the gut microbiome, changes in the immune system, more inflammation, both locally that goes into the brain and in the brain proper. You have changes in the production of neurotransmitters, not just acetylcholine, which seals memories, but serotonin. There are actually serotonin neurons without estrogen. They don't make enough serotonin, which is like the happy feel-good hormone. That's why after menopause, even women who had no earlier history of depression or anxiety, their potential for developing mood disorders like that doubles.

From serotonin is melatonin, so then we have these pervasive sleep problems, and estradiol also is a key player in maintaining the functioning of the master clock that sits atop the optic nerve in the part of the brain called the hypothalamus that helps to control all the time zones of our organs so that all of our organs are living in the same time zone. Basically, when you lose that estrogen, you lose the ability to stay properly timed and everything is like on a timer. Essentially, in a menopausal woman not on hormones, she is living a life of chronic jet lag, and we know that jet lag is associated with emotional problems, cognitive problems, metabolic problems, weight, every kind of problem, cancer increases.

[00:35:22] Jane: I can really speak to that because I've been on bioidentical pellets for a long time, probably since I was 40, but I can tell when they're wearing out and I need to get more because my sleep will become very light. My aura ring sleep scores, my readiness isn't good. It's really important. My question, this is fascinating, Felice, and it's delightful to find someone who's been in this business for decades like you have still so enthused about what you do. Thank you. I can tell you're passionate about it.

In reading to prepare for this interview, I noticed that in a 20-year-old woman, the average estradiol level is 600 something. Is that what we are aiming at for a woman to try to achieve that with bioidentical hormone replacement, a 600 level? I know mine is 160, so I need to be boosting it up in your opinion because it's not like a 20-year-old.

[00:36:17] Dr. Gersh: We have to be careful because there are different measurements, and even the measurement in the laboratory has changed. They use different assays now. We have to almost wipe out what we looked at just even a few years ago. The numbers have changed if we look at--what we'll say--more current numbers. Based on the new standard of numbers, because if you're having it done now, because otherwise, it'll be very confusing. I'm so glad you brought that up because they do have different ways of measuring with different machinery now.

Now, if you look at a normal menstrual cycle and we look at picograms per mil as the level that we…the numbers that we use now with the new monitoring system, typically, during the bleeding phase, which is the period, the shedding phase, the levels of estradiol will be well below 50. They could be in the 20s, the 30s, they'll be very low. Then it starts to rise and it can get to be like, close to 80, 90. Then you have this giant spike of estradiol for one day. That's what triggers the spike of LH, luteinizing hormone from the pituitary, which then triggers ovulation.

That spike of estradiol now, we used to say it could be many hundreds. Now they're saying it typically gets up into 300 something would be like the top. It's like, whoa, everything got downsized here. It would be like, we'll say 350, it might spike to. Then in the second half, after that big spike, it dips, then it comes back up and plateaus, and if you're not pregnant,

then it goes down again. Where does it plateau? Somewhere usually, in the 100 to 250 range, there's quite a bit of variety among different women.

I'm trying to work with people who are trying to start getting funding and set up a study of menstrual cycle reproduction, in terms of mimicking a menstrual cycle, which was talked about over 20 years ago, but it never got any real traction, but we have no published data. Theoretically, if you can truly mimic a menstrual cycle, that would be the best, but we don't have any published data on that at all. We're trying to get some studies.

Now what I'm doing while we're waiting and getting a little bit more data in general, I sometimes do some little modifications for some people who are like really gung-ho and I want to try mimicking a real menstrual cycle. In general, I'll try to get a level that is somewhere over 50. If it's not over 50, you're not getting where you need to go at all, and maybe up to around 150.

Now if someone gets up to 160 and they feel great, I'm not going to say, oh, well, we got to get you down 10 points. Because we know it's not really holding steady at that level all the time, every day. I typically don't want to go much above that because I'm looking for sort of averages. Then you have to look at women who have a uterus, how much bleeding they're having. We're trying to get them to have what seems like a normal light, in some cases better than they used to have because they had terrible periods, we'll say, but a normal light, just a few days, three, four-day period type of thing that they can put up with for the rest of their lives.

Because we are women, we were designed to have rhythmic hormones. If you give hormones the way they're given by most doctors these days, they're giving a tiny amount of estrogen and then continuous daily progesterone. Now, what's the point of that? From a physiologic point of view, nothing. From a convenience point of view, what they're trying to do is not have the woman have bleeding. Here's the problem. If you have bleeding, this is what I tell my patients, you should celebrate, because what does that mean? It means the hormones are working.

By the way, that's the other thing that I can use as a marker that hormones work after many years. You can get women to bleed. If their uterine receptors are alive and kicking, why shouldn't I believe others can come around? Because you can make a woman at any age, I don't care how old she is or how long she's been out of menopause, if I give her enough estrogen and then I give her progesterone, I can create bleeding. I can give her a pretend period, which is real blood, because her uterine lining is going to grow.

Once you embrace that, estrogen, the estradiol, that it has many wonderful effects in the body, which we've touched on, and one of them is to stimulate growth factors. Now in the uterine lining, the growth factors literally because it to grow. We use the word proliferate. Elsewhere in the body, that growth factor, like in the brain, brain-derived neurotrophic

factor, in the brain, those growth factors help to create neurogenesis, new neurons, repair of neurons, improving synapses, and improving the immune system, which is a unique implanted immune system of the brain, improving the health of the vascular system of the brain, the lymphatics of the brain.

All these things are part of growth factors. Think of it as maintenance, as well as growing. Of course, in the bone, you'll literally grow new bone. In the skin, you'll grow new skin. In some things, it's really about internal repair, autophagy, internal rejuvenation, but it's all about growth factors. If you give someone such a tiny bit of estrogen that you're not creating growth of the uterine lining, what is your end goal? Why are you giving the hormones? If it's just to suppress night sweats and hot flashes, it takes a pinch. It's amazing how little you can give to reduce that particular group of symptoms. If your ultimate goal is healthy longevity, to become a super-ager, then you're not getting where you want to go if you give such a tiny bit of estrogen that you don't even create any growth of the uterine lining because you're not growing or repairing or maintaining anything else.

Then when you have the progesterone, progesterone is like the yin-yang thing. When it comes to growth in the uterus, progesterone stops the growth or the proliferation, and then it causes the uterine lining to, like, flower. We call it secretory. It has a different effect. You don't want perpetual growth or you don't want perpetual flowering. What you end up when you give a tiny bit of estrogen and perpetual progesterone is you don't really get much of anything because they almost like cancel each other out, and you get very little growth and you end up suppressing the growth.

Progesterone down-regulates estrogen receptors. It's like the off mode a bit. It sort of suppresses it. Everything in the body with the beautiful rhythms works perfectly. This is not how nature made it. Nature doesn't give you a tiny bit of estrogen and everyday progesterone. There's no time in a woman's life that she has anything like that. Pregnancy is not like that either. You have humongous amounts of different estrogens when you're pregnant and humongous amounts of progesterone.

It's not like this at all. This is not mimicking pregnancy at all. What you end up with is a completely new creation that never exists in nature. You're doing a counterproductive thing from my point of view. You're not allowing the estrogen to do its job, which is creating proper growth and maintenance. You're suppressing it perpetually with the progesterone and you're really just like you're going in a car. You'd like to get to your destination, but the whole time you're in your car, you have the brake and the gas pedal both pressed at the same time to the point where you don't move, you're not going anywhere.

[00:44:41] Jane: What you're saying is, and it’s my main concern, I have many concerns, osteoporosis and heart health, but cognitive function is a real big concern. So the way I'm doing it now is wrong. I take 200 milligrams of progesterone every day, every day. You're saying, wait a minute, I've got the gas and the brake on at the same time. What do you

recommend that a woman does? When should I be taking the progesterone? What days to lay off?

[00:45:09] Dr. Gersh: 14 days of the month. If you're having a cycle and you're perimenopausal and you need supplemental hormone, that would be like you have a person who has low thyroid. They don't have zero thyroid. They have low thyroid. We give them supplemental thyroid. If you're still making hormones, but not enough, we would match the progesterone timing to when you're actually in the luteal phase. We would give it. But if you're not, if your ovaries are done, like mine are done--

[00:45:36] Jane: Mine, too.

[00:45:37] Dr. Gersh: --and you just can give it any 14 days that you want, I usually say the first 14 days because it helps women to remember day one is your start day of your progesterone. Now it still is better to be on any hormones than no hormones. I create little mottos. One of my mottos is any hormones are better than no hormones. Even taking them, like we'll say sub-optimally, is still way better than taking none.

Don't feel like, oh my gosh, no benefit. No, you still have benefit. You just maybe don't have optimal because when you think of the shedding, having that pretend period, but it's real blood, it's real shedding of the uterine lining every month. You're not just shedding the uterine lining. You're doing a purge. Think of it as you're purging crap cells everywhere in your body. The terrible cells. You're actually, it's like a purge.

Now, in a real menstrual cycle where you have different things going on, because you're getting the spikes and so on, you're actually turning on and off, and we don't really have the best data because nobody cares to study these things. We know in a real menstrual cycle, you turn on tumor suppressor genes when you're at your mid-cycle spike of estrogen and the mid-luteal point in the progesterone, you're actually turning on genes that deter the body from creating cancer. Tumor suppressor genes.

You also turn on and off other receptors. You make them work better or less better, like for testosterone, for thyroid. It's a little bit like when you have both hormones going all the time, all the time, it's a little bit like tachyphylaxis. It's like if there's a background noise, after a while, you just tune it out. The receptors just say, ah, forget it. It's sort of makes everything get numb. You need to have this refresher, like on off thing, when it comes to the progesterone. It turns on and off the receptors, you get like a reboot.

We have to try harder and we need to get more data. Of course, because right now, because we're not getting enough data, we have to work with a lot of mostly science. There's a little bit of data, not enough, a little bit that giving the progesterone rhythmically, like just two weeks out of the cycle, lowers breast cancer risk and cardiovascular risk. It's very limited data because nobody cares to do the research. We have a little bit of data

supporting that really is better for breast immune health, lowering breast cancer risk, and also for cardiovascular health. I wish we had more data.

I have patients that say having a period is a deal breaker. I'm just not going to do it. I will compromise and say, I'll take less hormone, maybe less benefit, but this is what I want. I go along with it. Every single one of my patients isn't agreeable to having a small bleed, which is like a pretend period every single month forever. They just say, nah, I would rather not do that. I don't want to do that.

Then I have no choice. Okay, so I'll do whatever people want because I really believe in my motto of any hormones are better than no hormones. Then I have to tailor it to them. There are a lot of individual, you might say biohacking, because we can give the same hormone regimen to 20 women, some will bleed, some won't bleed. It's not trial and error. It's just trial because it's not really error. We just have to see what works.

You have to get that special formula where you can put the gas and the brake on at the same time and not move. You have to put the progesterone and the estrogen into the person and not create enough growth of the uterine lining to create bleeding, which then that's what they don't want. Plus, if you have random bleeding it's worse than timed, controlled, expected bleeding. If some woman is having random bleeding, I have to investigate that. I have to say, I have to make sure you don't have uterine cancer. That's my job. I have to do that. Then I have to get an ultrasound. Sometimes I have to get a uterine biopsy. I have to do what I have to do because going on hormones probably lowers your risk of uterine cancer, but it doesn't mean you can't get that. You still can get uterine cancer even whether you're on hormones or not.

If you have random bleeding, I have to check it out. That's why it becomes an annoyance for people. They hate that. Then you just have to lower the estrogen and sometimes raise the progesterone. You just have to do what you have to do to keep the uterine lining from growing, which is what it does. That's its response. The easiest people, of course, to take care of are ones who've had a hysterectomy, but we don't recommend you have a hysterectomy because you have to work harder with your hormones. We just work harder with the hormones.

[00:50:36] Jane: That's a big deal. Thank you. Because I've never had that explained that way. I did not know that it was more optimal to bleed, even when you're quite old. I don't think many women realize this.

[00:50:49] Dr. Gersh: Here's a very important takeaway. Say someone is 65, okay? Okay, are all the cells in her body 65? Oh, no way. There are very few cells in her body there from the day she was born. Most cells in the body, the vast majority, will live a certain lifespan and different types of cells have a different expected lifespan. Bone is well-recognized. It tends to be seven years.

Each cell will live a certain amount of time. We want it to live a long time, right? Not in a bad way, not being zombie cells, but like healthy rejuvenated cells. That's the autophagy cell renewal thing. Every cell lives its own little lifespan and then it dies. Then it should be replaced from our stem cell pool, right? That's why we love our own stem cells. By the way, estrogen helps maintain our stem cell pool. Then we pull a new cell from our stem cells.

Every cell that's born in you is born with the same genetic programming that it had when you were 20 years old, even when you're 65. It's not like the genetic programming is different. If you can give every cell in your body what it needs, the right micronutrients, macronutrients, the hormones, all those things, then guess what? It will behave like any cell when it's born in your body, whether you're 65 or 20. It doesn't know how old you are. It was just made out of a stem cell.

You have to do everything in your power to maintain all of those things. Now we can't, no matter how hard we try, things are going to go somewhat south as we age, as hormones change, and our stem cells get older and different things in our environment and in our body. That perpetual problem that I fight like the devil, which is inflammageing, the chronic inflammageing associated with aging, which by the way, you can definitely fight by doing all the lifestyle stuff plus the hormones, you will maintain the biological age of a younger person as opposed to your chronological age.

Everybody's getting that concept now, right? You could be in a 65-year-old body, but the cells are acting like you're 40. My goal is to take every one of my patients and turn them into super-agers. What do I define as a super-ager? You're 95 and you can do everything you did when you were 35. That's a super-ager. That's my goal for me. That's my goal for my patients. I say, if you want to be a super-ager, so when you're 95, you can behave like you're 35, you have to do the following things. There's no shortcut. There's no shortcut and there's no magic pill.

Now there may be some pharmaceuticals that seem to be, it's analytics, these kinds of words, that help with giving mimics of fasting and that create autophagy and program cell suicide so you get rid of those zombie cells. Maybe there'll be some pharmaceuticals that are aging helpers, but all those pharmaceuticals that we're talking about, whether they're for mitophagy, for autophagy, for apoptosis, that it's programmed and appropriate, or this analytics, so that you can get rid of the yucky old zombie cells and all of that, all of those things you can trigger through different of your behaviors, like through time-restricted eating, exercise, having hormones, doing various fasting regimens.

They're harder than taking a pill or a shot. I do understand that, but we have the ability to access all of these pathways and create these things without a pharmaceutical that costs thousand-something dollars a month or more. I'm into first line doing the basics, like

maintaining all the lifestyle stuff and the hormones, and then doing all of that, I think you can be a super-ager without any of those other, we'll say, pharmaceutical tricks.

I'm not saying that everyone should shun those other things. I'm not anti-science, but I think that from a cost point of view and from a population point of view, it's not going to really work to give every single person an array of pharmaceuticals that runs into thousands of dollars a month and think that that's the best approach to health, so it just seems like we've got to do better than that as a population. People who are rich or motivated to go into anti-aging, whatever, and want to take all that stuff, that's their choice, but I'm fine to have it available. I think for the masses, that's not going to really be practical approach, I'm into very simple thinking, give every cell what it needs at every age and let it do its job.

[00:55:41] Jane: It's obviously working for you.

[00:55:43] Dr. Gersh: I'm trying to be a super-ager; I have to be a role model.

[00:55:45] Jane: Yes, I can tell. Estradiol, what is the best delivery mechanism in your opinion?

[00:55:51] Dr. Gersh: Well, it has to be not oral. That's the main takeaway. It can't be through the mouth. Anything that goes through an absorption, it could be, I typically use transdermal. That means through the skin. Some people could use transvaginal, which is actually a type of skin. Pellets are usable, and some people love pellets. I tend to not use pellets because I can't control the dosing at all. Like you said with you, at some point it's too low.

[00:56:25] Jane: Goes up and down.

[00:56:25] Dr. Gersh: I don't want there to be a few months every year for my patients when they're really sub-optimal. I'm really thinking that my own trend is going to be towards trying to mimic more of a menstrual cycle, which means at some point I'm going to want to have the estrogen, the estradiol, not to be static the same every day. I do have some protocols for that, but I don't use them widely because we haven't had lots of data. We have lots of science, but once again, we don't have lots of clinical studies because nobody's going to fund them. Nobody cares about them.

Fortunately, we can modify things by using existing products. It's not illegal, but I always am very clear to every single patient that, what do we have clinical data on? What don't we? What's the science? What are you willing to do? Because I never want anyone to do anything without clear, informed consent. I think the future, it isn't really now, but the future will be to mimicking more of a menstrual cycle with levels varying of the hormones. Obviously that's more complex.

Many women may say this is too much work. But then everyone has to make a choice, what is too much work? Is brushing your teeth twice a day too much work? Is going exercising every day? Is fasting? Is meditating? Whatever form of mind-body practice. Is changing your hormone dosing throughout a menstrual pretend cycle too much work for you? Everyone has to decide what they're willing to do. Are you willing to cook from scratch? Are you going to buy all processed food, right?

Everyone has to make their own priorities. If your ultimate real goal is to enjoy your life and to be the super-ager, then I think you have to just accept that it's going to take more work than just buying processed food, taking a shot or a pill, sitting and watching TV. It's just going to be more work to be a super-ager because we did not evolve to be super-agers.

When you look at the history of mankind-- and actually, a little over a year ago, I did one of my bucket trips, I went to Egypt. I'm going through all these amazing tombs and temples, and I'm seeing all these beautiful pictures on the walls, which they cleaned up. They didn't restore them. They just cleaned them up. They're phenomenal. I noticed that everyone in the pictures is young. I said, what is it with ancient Egypt? This is like 3,000 to 5,000 years ago. Did they not like old people? I checked on it. If you were a woman and you survived childhood, which obviously not everybody did, your average life expectancy was 35. Menopause wasn't a thing. Then I went to like the year 1200. Okay, if you were in the year 1200 and you survived childhood, what could be your life expectancy? Around 50. You got to menopause.

[00:59:23] Jane: Yes, in 1200.

[00:59:25] Dr. Gersh: It's only in the last 100, maybe 200 years, there were always outliers. There was the occasional person who lived to be 90. There were always outliers, but in general, we look at the general trend, women did not live-- through most of the history of earth with humans, did not even reach menopause. They didn't reach it. The ones who got to menopause, that was about the end of the line. That's why they made like Social Security, Medicare. They made it 65 because even then, not even 100 years ago, not even 100 years ago, they figured, well, you'd live maybe two years, 67, maybe. 65.

[01:00:00] Jane: Our grandparents.

[01:00:02] Dr. Gersh: Yes, your life expectancy after you hit Medicare age would be like maybe two years if you got there. It wasn't like, oh, we won't have to pay a lot of money because they won't live more than maybe one, two years after they hit Medicare age, retirement age, and social security. Then, oops, no, we're not. We're living long because of incredible scientific breakthroughs, but they're all like medical whack-a-mole. We have

this problem, we have this procedure, this drug. People are living with a lot of chronic conditions. We have Alzheimer's exploding, just horrific.

My goal is to be really cheap. I don't want the society to pay anything for my medical care, The goal is to live to be 100-ish, maybe you can go over, but to be in that range. Then maybe you deteriorate for three months before the end, and that's it. You're living like you're 35 up until you're like close to 100. That's a super-ager. That has never happened in history. There was no mechanism in the human body for that to happen. Nature did not evolve for us to be super-agers. Nature made us to live through making babies, raising them, and goodbye.

[01:01:15] Jane: We're breaking new ground.

[01:01:17] Dr. Gersh: We are, and we think everything. Do we want to have our limbs broken and back fractures? Do we want to have joints replaced? Do we want to have stents in our arteries? Do we want to be on eight pharmaceuticals? By the way, that's not ridiculous when I say that. There are many seniors on eight different pharmaceuticals. I don't know how they keep track of it. Do you want to be demented? Do you want to be able to dance and travel and think and do whatever you want and not live in pain?

Women have 80% of osteoporotic fractures. Like I said, two and a half times the incidence of Alzheimer's. They have more joint replacements for osteoarthritis than men. They have two to four times mental health challenges. They have more GERD. They have plenty of cancers. Cancers in women are not less, they're equal to men. By the age of 65, women have more high blood pressure, more strokes, more ruptured aneurysms, and die of their first heart attacks more than men.

We've got to get over this women are blessed with this great longevity because it isn't always a blessing because they do not have quality lives. Like you said, this is a whole new paradigm of life and aging. We never had longevity like this. We have to rethink if we want to play medical whack-a-mole or we really want to be proactive. It's so simple thinking. To be healthy, you just need to give your body what it needs. The nutrients, the hormones, the fitness, the love, the purpose, the sleep, reduce stress, poison control. It's not that complex. It's simple. It's just hard to act out. It's simple thinking, but then you have to actually do it. Our medical system is not thinking this way. Lifestyle medicine doesn't even exist in most medical practices. It does not. They'll send you out the door and say, eat healthy and move more, whatever. Good luck. That's it.

[01:03:20] Jane: Felice, you have been a phenomenal guest. Thank you.

[01:03:24] Dr. Gersh: It's my pleasure. Thank you for giving me a platform to spew all my thinking.

[01:03:30] Jane: You are so welcome. You have a great day, okay?

[01:03:33] Dr. Gersh: Thank you. You, too.

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