Estrogen, Progesterone, and the Aging Brain: Here’s a Smarter Hormone Strategy Transcript

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Hormones, Life, and the Menstrual Cycle

We evolved to create life, and that's what all these hormones are designed to support through optimizing health of every organ. And nitric oxide is made by, in order to facilitate a pregnancy, it stops the growth of the uterine lining.

so you don't have endless growth. The second half of the menstrual cycle is called secretory. It's like blossoming, the uterine lining blossoms. Think of like a teenage boy, he grows like weed and he's really thin, and then he stops growing, all these muscles develop.

He gets old, He fills out. That's the Uterine Lining. it grows and grows, then it blossoms, but you have to be careful. because you don't want to down-regulate all the growth factors all over the body.

It's a really gentle blend here of growing and stopping growth and balancing these hormones. Welcome to this episode of the Think Well, Age Well podcast.

I am your host, Dr. Heather Sandison, and I'm delighted today I have the joy of welcoming a true pioneer in women's health, Doctor Felice Gersh. She is an award-winning board-certified OB-GYN with a fellowship in integrative medicine and decades of clinical experience helping women navigate the hormonal changes that shape their lives from the reproductive years through menopause and beyond.

Dr. Gursch is one of those rare clinicians who can take complex endocrinology, gut physiology, circadian biology, and brain science.

Podcast Introduction and Guest Background

Her work has shone a light on how hormones influence everything from mood to metabolism to inflammation, cognition, longevity. She's also the author of several highly regarded books on PCOS, menopause, women's health.

A sought-after educator for both clinicians and the public. I had the privilege of meeting her at a conference and I've interviewed her in the past, always learned so much from Dr.

Gersh and just feel so privileged to have you here today. Thank you for joining us. Oh my goodness, it is such a privilege and we were chatting before coming on the podcast and, you know, just catching up.

And so I think this is a mutual admiration society because I love all that you're doing as well. Well, thank you. You know you have been talking about all of these things since well before it was cool.

The landscape and the conversation around hormones has shifted certainly since I've known you in the last couple of years, the conversion has radically changed.

with social media, some of the celebrity doctors that are out there on social medias, and some popular books that have been published. And I'm curious, like, can you just kind of take us through the last 10 years?

Maybe it starts in the 25 years, right, including the Women's Health Initiative study, but can just take through us the landscape of science, the media and our understanding that isn't just the female experience or the medicine, right?

There's like a cultural context to this conversation that I think not everyone's aware of. Oh, my goodness. What is history to many people is my memory.

So that's the advantage of having been there, done that, seen that. Back in the day, I was there when hormones were really growing in popularity. I went through training and so on.

And by the time the Women's Health Initiative was ended or came out, depending on how you want to look at it, was now, that was like 2003. So I'd already been practicing.

And, by that point, I was not using PremPro. I had stopped using it quite some time earlier. And they didn't have to do the Women's Health Initiative study with PremPro.

They just did because it was already in the works. It had been the most commonly utilized hormone, if you can call it that. You know, I call them endocrine disruptors for humans, but you know you use words different ways.

The Women's Health Initiative and Hormone History

And it wasn't commonly used and the precursor study that was called the HERS study, that was testing the use of PremPro that's conjugated equine estrogens with a chemical mimic-ish, actually endocrine disruptor agonist slash antagonist for the receptors of progesterone called Madroxyprogestrone acetate.

So that was what was used in the HER study, which tested women who already had established cardiovascular disease by having an event like a heart attack or a stroke.

So it was secondary prevention testing. And then that did not turn out so great. In that study, women had more heart attacks in the first year of use, but then it dropped off.

But then they kept using the same formulation of hormones for the Women's Health Initiative. By the time that was already in works, I had already switched to micronized progesterone and transdermal estradiol.

Estradiole is the estrogen made by the ovaries and conjugated equine estrogens are estrogen from a pregnant horse who has now put those hormones through the liver to conjugate them to make them water soluble so that they could be eliminated in the urine.

And it included what they call equal line estrogen. They're unique to horses and pregnant horses, never to be seen in a human female ever. It didn't have any estradiol in it, and it had predominantly estrone as far as a human hormone.

And estrone acts on one of the estrogen receptors, which is very important. But as everyone knows everywhere, whether you're in medicine or you are a consumer, is that dose matters and balance matters, right?

You know, so you can have too much of a good thing, then it becomes a bad thing. So estron is good when you have the right amount and the Estrogens because that's the other thing that gets very confused understanding that estrogen is not a hormone.

It's a family of hormones and it's often now being like lumped in with hormones that are in the estrogen receptor binding family, but they're not ever found in a human being.

So technically they're endocrine disruptors. An endocrine disruptor is something that interferes in one of myriad ways with the normal production, distribution, receptor binding, I think I mentioned that, elimination, detoxification of the hormone.

So it interfered in many of those different avenues. By the time the Women's Health Initiative came out, many had long ago abandoned the combination of hormones that they were utilizing because we knew, we already knew they we're not going to bode well for outcome.

Like, duh, you know, already know what they did. You were just saying this in your clinical practice. Yes. Women weren't responding as well. And we knew that the ingredients that they were testing, or we already knew from

previous data, from studies, that were not ideal.

They could suppress night sweats and hot flashes, but in terms of global health effects, they weren't ideal, it's that simple. So, but after that study came out, I fought like crazy to keep my patients on hormones.

I begged them, pleaded with them. There is no way that hormones, human identical hormones which is what I prescribed, that they turn from your friend to your enemy at a particular random age.

Because when you look at menopause, it's not the same age for every woman. In fact, there's quite a range. so-called normal, first of all, the definition of menopause, it's completely arbitrary and related to only one organ's impact, you know, from the hormones, which is the uterus.

Because it is not about the ureous, It is about ovarian aging and the ovariant hormone production and then loss of it. And women have had this question, I bet you have too, if they've had a hysterectomy, they say, does that mean I don't go through menopause?

Because I didn't have periods because I had hysterectomy. It's like, yeah, it's not about your uterus, whether you do or don' have a uterus, its about you ovaries aging and the loss, you know, the sort of up and down during the perimenopausal and then the ultimate loss of ovarian production of estradiol and progesterone.

So anyway, I fought about half my patients stayed on the hormones and about have did not. It was very personal to me because I was their clinician in the, you know, the cavalry trying to rescue my troops, from, the damage that was done by that study and all the wrong information and my begging them and some of them came back a couple years later and said, I give up.

I'll just take the risk. And it's like, what risk? I'm not giving you the stuff they tested. and I always use this analogy and i'm so happy i've seen other people use it.

So that's fine. It's up for grabs. i didn't patent it and it is like you do a study with strawberry flavored jelly beans The outcome is that you increase cavities, obesity and diabetes.

That's the findings. And then the recommendation from that study is never eat organic strawberries. I don't think we studied organic strawberry. So it's like, if you think of the human hormones as the organic, strawberries, of course, and then these strawberry flavored jelly beans was the prem pro, then duh, the conclusion doesn't match the study or what you studied.

You know, it's just been a battle, but in terms of his history. So I have been talking like sometimes to very avid listeners, sometimes into the wind, you know?

Because I was working in my office with my patients one-on-one as a clinician all these years and doing my little thing. But suddenly, for a whole bunch of different reasons, a lot of writers, medical writers.

Suddenly menopause became the thing, right? It sort of suddenly saw the light of day. A lot women are in menoppause. And they became a little bit more demanding.

Like, what can you do for me? Like I don't like what's happening to me, you know? I want just antidepressants. No, right. Because that's what really happened is that each symptom, because as you mentioned when you were like mentioning in the beginning about hormones, that estradiol and progesterone, which I'm talking much more about lately, they have receptors all over the body.

So I don't call them sex hormones which is how I was taught of them being. I talk about them as life hormones. They're the givers of life and the sustainers of the function of all the cells in our body and every single organ.

And you need it. It's like foundational, necessary, but not sufficient. Not, I mean, you can't, that's why I really abhor, this is kind of a strong word, But I do abhore a lot of what is happening in the menopausal sphere.

Like you know, hormone dispensaries. that aren't looking at the total human female that is being prescribed these hormones. So if we backtrack for a second, like you said, what's going on in the last 10 years?

Okay. What happened is, you mentioned hormonal starlets coming on the scene. advocating and writing books and getting all over social media and everything else.

And that is good, you know, it's good for them, I presume, but it is for women in general, for the population that's approaching in menopause to understand the significance of menopus.

So I think that They've done a good job of promoting more loudly what I have been talking about for decades. Nothing's new under the sun. We learn more about cell biology, physiology, but understanding that hormones matter.

They knew that in 1966 when that famous book, and I always get the words I can never remember which word comes first, feminine forever or forever feminine, whichever one it was.

I just have to just clarify it, but it's either feminine for ever or for every feminine. That was in 1966. We didn't know everything about receptors.

Why Menopause Matters Beyond Hot Flashes

I can assure you, we did not know that in 1966, but it was already apparent that when you lose your ovarian function, bad things happen to women. They knew that, and they knew by giving hormones, you had a reprieve, you did better in every which way.

You've just stayed more feminine, and you stayed healthier. So yeah, we knew way back. I mean, hormones go back into the 1800s, like the first estrogen, where'd they get it from?

They couldn't make bioidentical. That's a much more recent invention. They took cow's ovaries and ground them up. Just like if you've heard of desiccated thyroid, they grind up a pig's thyroid gland and put it in a pill, you know, that with cow's ovaries and then they did cows' placentas and they then did horse urine.

And the horse urine, Premarin, which Premrin, prem for, well, pre, P-R-E, for pregnant and marrin for mare, and in, for mayor and in for your in. Clever marketing, premarin, right?

So that came out on the market, was FDA approved, I believe in 1942, okay? That predates me, by the way. I wasn't there for that one. But the bottom line is that But it was recognized a long time ago that menopause isn't so great.

It doesn't matter that it's natural. There's a lot of natural things. That doesn' mean they're great, think of earthquakes, tornadoes, you know, yeah, they are natural, but get out of the way if you can, right?

So, we can't get it out the of menopus, it is universal. Doesn't it matter what ethnicity, what continent, and what social strata you're in. You're going to go, if your a female, live long enough you will go into menopia.

You know, how we're made, right? We're born with a fixed number of eggs and then we lose them and we can't make hormones because you can make estradiol or progesterone if you don't have any eggs.

It's like a cause and effect. That's a clear cause an effect, but what happened is the, I'll call them like the menopause starlets, because I'm not sure what to call, them in social influencers, whatever, you know?

And they have now brought to the public's awareness the was like reinventing the wheel. Okay, nothing new under the sun, but they're just broadcasting it.

And that's good because a lot of this got lost and menopause became only about night sweats and hot flashes and

for reasons that are kind of weird. And osteoporosis.

There's a generation of women who was basically denied hormone therapy after menopause and they suffered. Their relationships suffered, their families suffered their health suffered I mean, they really have.

They did a study, Dr. Sorrell. who is one, I don't even know him personally, but he's like one of my heroes. He was like me only, he was pretty renowned at that time.

And then until he like ridiculed, oh my gosh, what that guy must have gone through with the way he treated in the journals and everything else. But he an academic and he more out there than me, because I was in my office in Irvine seeing patients, raising four kids, and I wasn't out.

was just trying to do the right thing, and I read like crazy, I've read all the research, And I knew that it was insane. Just think logically. How could hormones, like if you think menopause, the so-called normal age and menopus defined arbitrarily as 12 months without any vaginal bleeding, that that point hits women, they call it normal, between 45 and 55. And the average is like around 51-ish.

But there's a big range and then early is from 40, just to 45, premature before 40 and late is over 55, so there is a lot of variation. So I say, how can it be logical that a woman who happens to unfortunately go through menopause at 44, her hormones turned evil on her.

And now if the woman doesn't go through menopause until she's 56, like that's okay. They don't like say, oh my God, when you hit 50, we got to take out your ovaries.

You're going to kill you. Of course not. It's like wild. In fact, now they're saying, and this is appropriate and inappropriate, that if you go into early menopus and they are saying even like in like 45 or 46, which is actually considered so-called normal, that you should go on hormones.

Like if you have menopause in your forties, you shouldn't go in hormone therapy until you hit at least like 50 or 51 and then you could stop it. It's like, uh, because suddenly they became evil at 51, but they were okay at 49. I mean, some of the logic is still very much lacking, I can tell you.

Yeah, there's also this logic around birth control pills versus hormone therapy with menopause. I think that birth control is less safe, right? And obviously having a child and figuring out contraception is an important thing and maybe it is okay to have some risk associated with that.

But I think that when people hit menopause and you're talking about sleepless nights and night sweats and losing your sexual relationship with your partner, you are talking depression, mood changes, there's so much more than like you said that just the hot flashes and nights sweats.

Well, I would love love to go over, I hope that we'll have time to wrap up the history and the last 10 years and then really go into what to do, because that's really part of the what-to-do, the birth control pills versus bioidentical hormone use and so on, in terms of wrapping up like the historical stuff.

So, you know, in the last several years, Menopause has really become like just the spotlight is on menopaus. And there's all these books and it's being talked about.

You know they have New York Times articles talking about, well, we should accommodate. We should have a workplace accommodations. It's like change rooms, restrooms, showers.

treatment, not accommodation. Let's not think of menopause as a disability because that's really harmful to women who are trying to further their careers.

Like employers have to be burdened with all kinds of rest stops and change rooms and all this craziness instead of just women getting proper treatment.

But what's happened, which is very good, as I was saying, is that the issues surrounding menopause, the harms of menoppause in terms of what happens in the different organ systems, that's really being vocalized a lot now.

So, although not everybody knows yet, but a lotta people know there's problems with menopus for every organ system, or at least they know a little bit more, you know, it's variable, 15 years ago when still it was demonized.

But still, the vast majority of women are not being prescribed hormones. And this is where it gets into the next chapter. As we have more and more consumers, and honestly, a lot of what's happening in menopause is being consumer-driven, because the doctors are always getting the word more at the medical societies, they're educating more And I do that as well, you know, trying to educate doctors that this matters and then what to do.

But the what-to-do remains a big problem. If we figure over the next couple years, we'll be almost, and I'm hoping, universal. that every consumer and every doctor understands the consequences throughout the body of loss of ovarian hormones, estradiol and progesterone.

Bioidentical Hormones vs Conventional Regimens

I'm hoping that will happen. Then we get into the next chapter, which is a huge chapter. First thing to solving a problem is to, number one, recognize there is problem, right?

Number two, define and understand the problem And three, deal with it in the best possible way. So now we're at a stage where we recognize more and more, like, you know, going back, those of us who were there, and like I mentioned Dr.

Sorrell, he put out a paper talking about all the unnecessary deaths, like you talked about, all of the problems for women, this whole generation. I call them the lost generation, you know?

Like in Peter Pan, there's the Lost Boys. Well, we have the last generation of women. And he talked that and how many lives were lost using some kind of, framework and statistics that I don't know how they modeled that model.

But in any case, they came up with somewhere between, and this was years and years ago, 50 and 100,000 women would die prematurely because of the reaction of doctors to stop prescribing hormones after the Women's Health Initiative study came out.

So pretty, and that was a long time ago, you know. So women not only have had poor quality of lives, like you said, in all these medical consequences, but many of them, they ended their lives earlier than necessary with chronic diseases that they didn't need to suffer from.

So that's a very big deal, but getting back into then what to do about it. And that where I'm putting, because now there's so many people besides me talking about all the harms, although I still like to talk about because there are still many that don't know the nitty gritty of what really happens when you lose these hormones.

But there is more and more people talking, at least somewhat, And, but then what to do about it, I think is a big problem. And what I was saying is that in the last several years, where there's a desire and a demand, there will be someone fulfilling that, right?

And that's called capitalism and, you know, business. and I'm not against that at all. So there has been a lot of entrepreneurship in menopause world and involving hormone, do I call them hormone distributors?

You know, they are, a lot of them are online, not all. Kind of. Well, I don't want to name names, but there's a bunch of the them out there. And then there are some people also have offices, and their goal is to obviously make money and also hopefully, because I mean I do not know them personally, hopefully to do some good.

I always think people have good motivations as well as financial motivations. But here's the problem. They're dumbing down women's physiology. I wish it was so simple, but we are complex creatures, we ladies.

Oh my goodness, hormones aren't and don't just like come and then you have the same amount every day, a little bit of this, little of that. That is not the way the female body works.

And so we, everyone now understands that there are rhythms, like everyone's heard of, you mentioned earlier, the circadian rhythm. That's based on the 24-hour rotation of Earth on its axis.

It's fascinating. There are creatures on Earth like humans who are diurnal. We're most metabolically active in burning energy and doing all kinds of activities with our brain that are focused, cognitively aware, and we're awake.

awake during the day, that's diurnal. And then you have nocturnial creatures like owls and rodents, they do most of their activity and they're awake at night, okay?

But what is not being well recognized is that females not only have circadian rhythms, of course males do too, but we also have lunar rhythms. It's so weird, but it's not an accident that female humans developed a 28-day menstrual cycle and the moon cycle is 28 days, just like we have circadian rhythm based on the Earth's rotation for 24 hours.

It is so amazing that you can take us and put ourselves in outer space like Star Wars and Star Trek, but, you know, our genetics are still what they are.

We know that when you add in associated genes with the genes that are directly clock genes, like 90% of all the jeans in our bodies are related or are clocked genes.

That's how much we live on a timer, okay? And when a female who has normal menstrual cycles, the hormones are not static, low dose. And that is so simple to prescribe.

Any person can learn how to do that, right? You don't need to have a lot of education in female health. You do not have to know how do an exam. you do have know about anything really much.

We just have memorize a few protocols and a what ifs, a you know. So the standard now has become, and this is very upsetting to me. The standard hormone therapy protocol is tiny doses every night of progesterone.

And I say tiny because it's given orally. When you take progeterones oraly, the history of Progesteron is interesting. They couldn't make Progeteron initially, just like they couldn estradiol, so they had to come up with a fake one that they could manufacture, and they came up what became a made-up word called progestin.

That's what they put in birth control pills, projestins. In fact, birth-control pills work because of the proestins, the estrogen. that's added, which typically, but not exclusively anymore, is ethanol estradiol.

That's not part of the mechanism at all, not even a little bit of how they work to prevent ovulation in pregnancy. It's all from the fake, we'll call it fake progesterone.

Progesteron is a single type of molecule. in a family that they sometimes call progestogens, which includes the fake ones, the projestins, and the real one, projesterone, they call them progetogens.

So the faked ones are the what's in birth control pills and what they used in PremPro, medroxyprogesterone acetate. And when you give birth-control pills, They tried different arrangements where they changed the dose to try to have better cycle control or this or that.

But most birth control pills now the default went back to the same dose of estradiol and a rather ethanol estridiol or some other estrogen that they're using now.

along with the progestin every day. And then they sometimes do, sometimes don't, give just a few days off a month. Sometimes they don t, you know. So there's a variety of those arbitrary kinds of things to create bleeding or to prevent breakthrough bleeding.

That sort of became a thought process that you could just do that even for hormone therapy in menopause. The typical dose And this actually is going to get into brain health and cognition.

And when we talk about that more, is that they give a little bit of progesterone. I mentioned the history of the progeterones. Finally, they were able to manufacture progestrone.

But uh-oh, when you took it orally, the stomach acid digestive enzymes broke it down into amino acids. No, because it's a protein, right? So it just broke it down into amino acids and you didn't get any progesterone into your bloodstream.

Then they came up with this process that's called micronization, and they made micronized progeterones that allowed it to get through the digestive tract without being broken down to its component amino acid.

But when you do that, it goes to the liver. The liver is the master organ of metabolic transformation. It turns one molecule into another and also proteins.

And what does it do to progesterone? When the oral micronized progeterones get into the liver, 80% of it is converted into other stuff. The other is called metabolites.

The main other stuff, the main metabolite, is a molecule that is not progesterone, but it comes from pro gesterones, which is called allopregnanolone.

Now, you also get some proesteroin that doesn't get broken down by the liver, But it's not very much. It's like 10, maybe 20 percent. And when you measure levels in a normal female who's cycling, the progesterone level, when she's making it in the second half of the menstrual cycles, is 10 up into the upper 20s.

Now, what levels do you get from oral progeterones? Typically, there's variations, of course, but it could be one and a half, two, maybe three. So it's way, way below what you would see in a healthy cycling woman.

Progesteron is very important. We'll talk about it. isn't just there to create a period and to prevent uterine cancer. In fact, that's what most gynecologists, it's very sad to say, think progesterone does.

That's it. It's all they think about it, and that is why they say if you don't have a uterus, you do not need progeterones. I just wrote an article, hopefully it will get published, on why every woman with or without a Uterus needs progeseron.

But she does not just need Progesteron, she needs it at the right amount. Everything is dose dependent, right?

Brain Health, Progesterone, and Allopregnanolone

If you can say exercise is great, but I only get five minutes a month. Uh-oh, a little suboptimal dose of exercise there. Or I love vegetables. I eat one spoonful a week.

It's like dose matters. About the there was a recent study in the last couple of years, it was the women over 65, about 10 million women that showed basically the benefits.

There was, I think, a 19% reduction in all-cause mortality for women. Over 65 on on hormone therapy. And part of what they described was that women, when you added progesterone, you reduced the risk reduction.

So you basically you reduce the benefits. And so if you could use estrogen without pro gesterones, that that would be more beneficial. What I hear you saying is that no, we need pro testosterone, even if we don't have a uterus, and that we're going to get benefits from that addition.

Well, there's a couple of things with that. Yeah. jumping into that. So remember, everything is dose-related. The conventional clinics and online programs are typically, I'm not saying that there aren't exceptions.

I haven't done an exhaustive study of everything that everybody's prescribed. But generally, they get a very tiny dose of estradiol transdermally. They'll start with the patch dose, the lowest dose 0.025 milligrams.

That is such a low dose it stays way in the menopausal level of estradiol. You're not even getting anything. It's like measurable. Your hardly can measure any change.

That doesn't mean that people don't feel a little better or that it doesn' do any good, but it's all good as dose related too. Like what's your goal? And it's not even approved for suppressing night sweats and hot flashes, but even a whiff, it seems, over time of estradiol will do some good in that department.

It's always hard to say if it is different than placebo because placebo effect is 50%. And then they give that little dose, usually 100 milligrams, occasionally 200 of progesterone.

And here's the problem with that. So there's a number of problems with these routines of regimens. When you give oral progeterones, like I mentioned, you get very little progesterone, but you a lot of other stuff, the metabolites, a dominant one being allopregnanolone So allo-pregnenolones is very good for the brain.

except when you have too much, okay? So there's data that allopregnanolone at the right amount, and it's converted from progesterone in the brain, that's why it is called a neurosteroid, because it in in brain.

And progeterones is a neuro-steroid too. It's also made in a brain but not anywhere in enough quantity in menopausal women to do what it needs to. So allo-pregnantolones in right amounts at right time, is actually neuroprotective and there's some data suggesting it may help treat or prevent Alzheimer's.

So very good for Rafer, allopreg, not alone for that. It activates the GABA-A receptor. GABAA is a neurotransmitter that is known as inhibitory. So it like inhibits focus and memory and it makes you sedated so you can fall asleep.

That's why people, you know, like GABA. Now what drug activates GAB A receptors as well? A different spot, but it's a very similar thing. tranquilizers, benzodiazepines like Valium and Xanax.

We know that if you chronically utilize them, that's not so good for cognition over the long haul. No, we don't want to take sleeping pills like that either, like Ambien.

That's a good thing for chronic use. Now, here's the thing. Allopregnanolone is very comparable. I mean, they actually work in the same way, just a different site on the GABA-A receptor.

Too much of a good thing is a bad thing. So there's rat data, you know, of course there is no human long-term data that if you chronically activate GABA with allopregnanolone, You get rat dementia.

You know those little rats, they can't find their way out of any maze whatsoever. They're lost in the maze. Okay. Now what about humans? We don't have longterm on dementia, but we do have data showing it can impair memory formation.

Oops. That's not so great. So those are a problem. So if we look at women who are on progesterone taking that kind of regimen, well, maybe that's not so great for them.

They're not getting progeterones. Now, they're getting very little progesterone. Maybe it's enough to prevent endometrial hyperplasia when you keep the dose of estradiol really low.

And we'll talk about why this even became so popular as a hormone regiment. And the other problem is that progesterone, and this is actually why they give pro gesterones every night a little bit, because there is so much fear of bleeding.

Like I'm a gynecologist. I've not afraid of the uterus. You know, it's like my friend, you know? I understand the Uterus. designed appropriate bleeding from hormones, like a normal menstrual cycle, or if you give hormones

exogenously from outside to create a similar scenario within the uterine lining, that it grows and then it sheds.

If you think of a normally menstruial cycle the first part, you only have estradiol and the amount starts very low, day one of the menstruation cycle is the 1st day of period, the estrdiol is very little, it's in menopausal range usually, and then it comes up and you get this spike of estradiol and that triggers a spike in luteinizing hormone and causes ovulation.

And then in the second half of the menstrual cycle, and this is an area that I'm really pursuing a lot more now, the is produced in a higher amount than it is in the first half, the follicular phase.

And that is when progesterone is also made. So in this second half of the menstrual cycle after ovulation, The ovary produces this structure that's called the corpus luteum that still makes estradiol, but it also makes a lot, a lots of progesterone, A lot more pro testosterone than estridiol.

But the amount of estrdiol also rises. And I think that's why women do well in general in the luteal phase, but not all. Some women have PMS, and there's a couple of different reasons for premenstrual syndrome.

And one of the theories is they don't make enough estradiol, is that they have a paradoxical effect to allopregnanolone, where they actually have an opposite effect.

Instead of it being calming and like sedating, because it's actually use of allopregnanolone as a drug for very short-term, very high-dose postpartum depression.

A synthetic form of alopregnanolones is used to treat post-partem depression, but not for long. Now, here's an interesting thing about that drug. There's two, oral and an infusion.

They're controlled substances, they're scheduled for controlled substance. They are treated by the DEA, Drug Administration Enforcement, and they are kept track of.

You know, you have the special prescribing type of thing for control substances like Valium or Xanax. It's a special way of prescribing it. Dr. Krish, I think for our audience, you know, it's mostly post-menopausal and really interested in how hormones affect the brain.

And I know that the nitty-gritty of some of these other options is super fascinating in the science, but I just want people to have a takeaway of like, all right, how do these hormones impact my brain, particularly if I And maybe 10, 15 years past menopause, I was in that lost generation.

I did not have access to hormones. What are your thoughts about the importance of potentially initiating hormone therapy later on? This is so controversial.

Now, in terms of like the article you referenced, and this is why, because you said like, why is it that They said that if you add progesterone, somehow you don't get as good an effect.

And these were women who were not starting hormones at 65. They'd already been on them for some time preceding that, like years before that. And what I just want to in a nutshell say, the reason why the women may have done worse who were on the so-called progesterone is that many of them were actually on not real progeterones, because they misuse that word all the time when they're talking about projestin, madroxyprogestone acetate.

Madroxyprojestoneacetate in the brain and in arteries, think of it as an anti It's an anti-progesterone. It blocks the production of a very vital gas called nitric oxide.

it actually blocks its production, and that is really bad for vascular health and for brain health. So the women who were not on real progesteron, they were on anti progesterone, so of course they did worse.

Now here's the other thing about real The way that it works, and the reason I brought up the menstrual cycle, is that when you make progesterone in the all progeterones, it downregulates the action of one of the estrogen receptors that's called alpha.

Dose, Timing, and the Menstrual Cycle Analogy

Now, alpha receptor is really important for many functions in the body, and one of them is the creation of growth factors. Now this has a big implication for the brain.

In the uterus, the growth factor causes growth of the uterine lining that we call proliferation. So, if you have enough estradiol, of course, you will grow the uterine lining.

Now, in order for a woman to successfully become pregnant, and that's what the hormones are all about, it's about creating new life, but inorder to maintain a healthy female to create new lives multiple times, we have to have functioning healthy organs everywhere all over the body.

That's why these hormones about functioning and health of every organ. not just the reproductive ones, because you will not be successful as a reproductive female if you have unhealthy brains and arteries and everything else.

And so we have to understand the purpose. That doesn't mean we all have unlimited babies at all, but it's important to understanding that we evolved to create life, and that's what all these hormones are designed to support, through optimizing health of every organ.

And nitric oxide is made by, there are some different pathways, but most of it is by action of an enzyme called nitroxide synthase, which is activated by estradiol and by progesterone.

A lot of people don't know that. But when you have progesterone in order to facilitate a pregnancy, It stops the growth of the uterine lining so you don't have endless growth.

And then the second half of menstrual cycle is called secretory. It's like blossoming. The uterus lining blossoms. Think of like a teenage boy. He grows like weed and he's really thin.

Then he stops growing all these muscles. He fills out. That's the uterine lining. It grows and grows, and then it blossoms. But you have to be careful because you don't want to down-regulate all the growth factors all over the body.

and balancing these hormones. So to that end, the ovaries make more estradiol in the second half of the menstrual cycle, I believe, to compensate for the action of progesterone down regulating the function of alpha receptor.

Now, what if you have a tiny bit of everything? You know, none of this stuff is going to come into play properly. But the whole point of why the conventional practice is to give a progesterone, a small dose of pro gesterones every single day.

is to downregulate the growth factor production of estradiol for the uterine lining because they don't want to have bleeding. They dont want have to bleeding, but here's the problem.

Those same growth factors that grow the uterine linings create growth and maintenance, not just growing, restoring, rejuvenating, maintaining the brain with these peptides.

And everyone knows peptides, that's another whole story. They're like so trendy, but we won't get into that too much. But there are peptide in the brain that are required for brain health.

And you need to have estradiol to create these growth factors like brain-derived neurotrophic factor. and nerve growth factor, and other things that people don't even think about as important for the brain, like oxytocin, vasointestinal peptides, so many peptide.

Peptides that are involved in mitochondrial function, which estradiol is critical for creation of energy. And you don' t want to have a brain deprived of ENERGY.

It's not going to work well. Well, you need these growth factors. So what are these hormone regimens that we're giving doing? They're down regulating one of the main benefits of estradiol, which is the creation of growth factors.

Now you cannot segregate the uterus from the brain and all the other organs in the body. So if you give estrdiol enough to create growth, factors like grow bone, like maintain, restore arteries and everything else, then you're going to do Whether you like it or not, you're going to grow the uterine lining.

And if you grow it, the uderin lining, You must shed it. To that end, we have to have cyclic progesterone so that we create a period. You have frame it in your mind of, this is why I'm doing this, because seeing this Instead of saying, this is so annoying or this so unnatural, everything we're doing is unnatural so that you have naturally good functioning organs.

So I'm over that part. Everything in medicine is un-natural. Every drug is on natural. every procedure is a natural, so we want to be as close to naturally healthy.

That's the point. even if we use unnatural means like maintaining hormones after menopause. And the bottom line is that the current regimens are not designed for optimal brain health.

This is like a huge takeaway that I want everyone to hear, is whether we like it or not, this is how we're genetically made. It's like people who don't like to sleep.

Well, I'm sorry, but sleep is like really important, you know, that's when we clear out the gunk from the brain, with the whole lymphatic system, which by the way is modulated by estradiol, duh, everything is.

And progesterone is also like critically important. Progestrone. Is neuroprotective as well. An estridiol is neuro protective. Now. So, but remember, dose matters and regimen matters.

And this is where I'm very, very happy that we have all these people out there now extolling the importance of hormones, two thumbs up and the negative impact of Menopause, two thumbs up for all of that conversation, but the problem is what to do about it.

And I really absolutely believe we need more research. I'm the first one to get on the bandwagon. Of course we needed more. But even without the clinical studies, we have a lot of science, a whole bunch of scientists.

We know how these hormones interact to up and down regulate different hormones and their own receptors. the impact on gene expression, epigenetic modification, and all these gene expressions, including tumor suppressor gene, expression when you have the differences in the varying amounts of estrogen and progesterone.

I mean, we really need more data, absolutely, but even without the clinical studies, We know science and we know that estradiol the product, you know, enhances and creates the production of growth factors, which are essential for life itself.

And most of this stuff, by the way, that are peptides, a lot of them, I research everyone that comes out, most are modulated by estradiol. Okay, so if you have enough estradiol, you'll make the right peptides at the time, and they'll work because estridiol also is very important for receptor function.

And so is progesterone, very for the brain neurotransmitters. So if we talk about older women, this whole group, the lost generation of women that now they're told, lady you missed the boat.

That boat left a long time ago and you're too old. Well, if you think about why are they too old? What is the potential problem? Well a lot of the data, but not all of it, comes from the Women's Health Initiative, which used PremPro.

So everything from that study is not applicable to bioidentical hormone use because they're just totally different molecules and they have different, they are just different and have effects on receptors.

Some of them block, you know, like Madroxyprogesterone acetate can actually act as a progestrone. blocker. When you take conjugated equine estrogen, aka Premarin, you get all these weird horse estrogens, plus you predominantly estrone, which is all alpha.

Although alpha matters, it's just too much of a good thing. At that point you're not getting the balance of the estrogen receptors. being operated upon.

So what about old women then? We know that the Women's Health Initiative data where they showed women who were like 70 plus, you had to get all the way up into that age group, 70-plus had higher rates of strokes.

Well, we know the premarin increases the risk of blood clotting 400% above baseline. That alone could explain it. The same thing with dementia. They could have these little micro strokes from having extra cloting.

and it blocks nitric oxide. You know, the metroxyprogesterone acetate blocks nitrogen oxide, so that's a bad thing because you need nitroxide for vascular health and for brain health.

So there's lot of reasons why that wouldn't have been like great for older women. But what about not using that, using bioidentical hormones? Well, this is what the concern is.

And the data is actually mixed and a lot of it is in rats, and that's part of the problem. There's not a lotta human data. The human that is, is mostly in vitro, like they'll take arteries out of their body in very unnatural situations.

and then they'll infuse them with estradiol and in one infusion and they will say, you know, I don't like, the artery didn't dilate as well. But in terms of I've done a lot of research on this and, in once study, where they took out the uterine arteries from women who had hysterectomy, so they have the uderin arteries, it's hard to say if those uterin arteries are the same as your other arteries like your coronary arteries because they didn t take out people's hearts.

to check their coronary arteries. Women, enough women at different ages had a hysterectomy, so they used the uterine arteries as, but not in the body, this is outside the buddy.

And what they found was when they took them and then they infused estradiol, that the only age where they didn't get as good a response of dilation, you know, they veiled with the artery like was relaxed and opened up to allow good blood flow, was women 80 plus.

So maybe there is something about 80 plus. I don't know. We don' have lots of data. That's like one study using uterine arteries outside the body. And then there's a mixture of datas.

There's some that show good response, less good respond. So what's the concern anyway? that one of the concerns is that the estrogen receptor alpha. Now, I mentioned estrogen-receptor alphas.

There's three estrogen receptors that are in humans, alpha, because we love Greek letters, and beta. And then there's a G-protein-coupled receptor that works only on cell membranes.

The alpha and the beta are primarily, but not exclusively, nuclear receptor activators. So they work in the nucleus of this cell to create different proteins and or peptides and but they also now we know work on the cell membrane to create rapid response.

It takes quite a bit of time to make these proteins or peptides. And the difference, by the way, between a protein and peptide is just the length of the chain of amino acids.

They're just all chains of But the alpha and the beta also work on the cell membrane to have very rapid effects, and

they also interact with one another.

Late Initiation, Aging, and Estrogen Receptor Questions

If you have a lot of beta activation of the receptor for beta, It downregulates the receptor for alpha, which is a key thing that happens in pregnancy for another story for a another day because pregnancy is very unique time.

We're not trying to ever mimic pregnancy in women who are in menopause. That makes zero sense. And the G protein-coupled receptor, which is really important for brain health and vascular health, we're just learning more about it. That's the most recently discovered receptor.

Then we have all these other weird receptors, like receptors to estrogen metabolites, to methoxyestradiol. That's a metabolite. It's made from estrogen in the liver, and then it actually has its own receptors.

Very involved in energy production. And then we had these others that used to be called orphan receptors now called estrogen-related receptor. We don't even know what binds to the receptor, but we know if you don' have estradiol in the vicinity, it won't bind and the very important actions won' occur.

So estridiol has so many different like side issues and so on. And so all of these are important. For vascular health, it's very important. For bone health muscle health and also works in the hypothalamus.

It's the dominant receptor activator in hypothalmus of the brain that activates temperature and the autonomic nervous system and appetite regulation, energy utilization.

So it is very, very very importance. And also related next to it the hippocampus which is important in memory formation. So alpha is very, very important in arteries.

to make nitric oxide, it's very important. But here's the thing, what they're saying is when women get old and they are over 60 or they 10 years out from menopause, that their alpha receptor becomes malfunctional or less functional.

And so you have paradoxical effect and when you give estradiol, you'll get a bad effect instead of a good effect. And this is a very complex sort of concept, which, by the way, has not been proven in clinical studies.

And in fact, if you look at the clinical study that exists in older women, like the ELITE study, That's E-L-I-T-E. Of course, the letters stand for something.

But it's called the ELITE study. They took two groups of women, women within six years of menopause and women over 10 years out. And then it went for a few years.

The used, of course the wrong estrogen because these were created studies by cardiologists who didn't get it. They used one milligram oral estradiol, bad choice.

They used progesterone gel that was too small and for too few days. But even despite that, it showed no harm. No harm! They didn't show benefit in that group, in the older women, but the point is they didn' use the right hormones or the dose or anything.

It showed NO HARM. So that is a really good study from that perspective. You know, we don't have any clinical data that it really hurts women. We do have data from the HER study that used PremPro that in these women who had a heart attack or stroke, when you gave them Prempro, that combination, for the first year and the 1st year only after they started on these hormones, they had higher rate of heart attacks, I believe, strokes.

So, but then it actually, the rates started to go down the longer they were on it. So it's kind of a weird kind. It's like it knocked off the women who are really like on the edge.

And then after that, it seemed to even be beneficial. But that's using Prem Pro. Who knows what that means for human identical hormones. So the bottom line is that this is actually now a huge project of mine.

So we'll have to reconnect because I'm looking into it like, okay, so what if there is this hypothetical that you have some injury or damage or dysfunction of the alpha receptor of estrogen so that don't get the benefits when you give estradiol and you get negatives?

Well, then the question is, how do we even know that's happening? Because all women are not the same at age 60. We know, that right? Everyone's not same.

And what about younger women who have a lot of inflammation? because this down regulation of the alpha receptor seems to be related to inflammation. I'm sure that word comes up all the time in your world too, Heather.

You know it's like inflammation, inflammation well, what About younger woman who just have inflammation you know, should we do something about them, too, to try to improve their health of their estrogen receptor alpha?

So I'm looking into the case, so what can you do to, say, improve your health, of your estrogen, receptor, alpha. Well, interestingly, one thing could be you give estradiol and project because that can rejuvenate by also lowering systemic inflammation and creating beneficial You know, everything, you know all the healing mechanisms that come into play.

Both estradiol and progesterone modulate the immune system. Progesteron is highly anti-inflammatory and estridiol turns on and off inflammation as needed.

So then what about also lifestyle things like a lot of the things that you advocate for? They seem to increase the benefit to and function of estrogen receptor alpha.

So maybe you can't give estrogen in a vacuum. Maybe just it's necessary, but not sufficient for anything. You have to include all the lifestyle things.

you have include fitness and stress management and sleep management, and nutritional management avoidance of toxicants, look into chronic infections, all this stuff that You do.

That's activating and improving the function of estrogen receptor alpha. Maybe that's a big part of what you guys are doing, you know? And we all need to band together and look at how can we evaluate the functions of estrogen receptor in clinical practice, not just in some research lab.

not just using rats. How can we actually measure this and then how can then follow it? You can't monitor what you never measure. What kind of substitute can use to monitor?

Maybe inflammation markers, maybe looking at vascular dilation, like flow-mediated dilatation. Maybe that would be a good measure, I really think so. And in fact, there's some studies, very small ones, that have shown that If you give estradiol, this is so interesting, if you to a menopausal woman or one that has no estrdiol.

If give her estridiol she will always, well they didn't do like 80 year olds, okay, but they will have vasodilation. No estradiol. The artery constricts.

You add estridiol, the artery dilates. Okay? They've shown that. That's like, but not in 80-year-olds. They didn't take 80 year olds. Then what happens when you add progesterone?

This is real data from little study. If you have a certain amount of estrdiol and then you had a small amount progesterone, The arteries doesn't dilate.

And if it's already dilated because you gave them the estradiol, then you add the progesterone, it constricts. Uh-oh. But if you increase the estradiole, you increased the esrdiol to be more similar to alludial phase estrdiole.

And in the study, they actually measured estridiol levels. They, and they, actually gave estrediol. To mimic the levels, a typical level first. in the follicular phase when you only have estradiol, and then when the progesterone was added to be higher to mimic the dose, the level you would see in luteal phase.

And then they added the pregestrone and guess what? The artery stayed dilated. So no estradiol artery constricted, add estrodiol, artery dilates. Add progesterone, but not enough estrdiol the artery constructs again.

The estridiol higher, the arteries dilate, and then add the projesterones, arteries stays dilated. So this is all about dose and regimen. Dose dependence.

I am now looking at moving forward, giving a higher amount of estrediol and a lower amount of estradiol, depending on whether the progesterone is being used for the first weeks of the cycle, no pro-gestrone, the second two weeks pro gestrone.

Then how about giving the pregestrone optimally, not this oral stuff, that's a micronized oral, where you get very little progesterone. And remember, progeterones increases nitric oxide, but it's all this beautiful dynamic, because progestrone down-regulates the alpha receptor, which is key to nitroxide function, okay?

So it is like this, beautiful balance. It's like really very, you know, elaborate, yeah. Yeah, it complex. But I think that we need to get away from this little bit of estradiol and little of oral progesterone every single day, because that is not physiologically compatible with any time of a woman's life, ever.

Key Takeaways on Hormones and Healthy Aging

And it's all designed not to bleed by giving too little estridiol, and then oral-progesteron, which gives you too much metabolite, like allopurinanolone, have a negative impact on memory and you're not getting enough real progesterone, which is beneficial, but we have to maybe increase the estradiol to compensate for the effect of pro testosterone so that you don't down-regulate the production of nitric oxide or factors for other parts of the body.

So, it's just a really interesting thing and we definitely need more research, but just going to this default little bits of everything, in daily same amount, that makes zero sense.

That makes absolutely no sense, so- That's better than nothing, I hope, from a lot of women. You know what? I always said that, you know? Any hormones are better that no hormones, But when you look at the long term, It's hard to know how the benefits and the risks are balancing out over the long haul because it's just hard know because you know you're having progesterone down regulating the estrogen receptor alpha which makes the growth factors which are so critically important for brain health.

So that's maybe what they haven't yet shown that giving hormones in the way that we're giving them, like, prevents dementia. They haven' shown them. Maybe it's because you've given it wrong.

It's not the hormones, it how you're doing it, just like exercise. You can prove that exercise does nothing useful if all you test is five minutes a month.

I'm sorry, dose matters. Dr. Gersh, thank you so much for taking on this very rich and fascinating journey today. You have a rare ability to walk us through super complex women hormones, everything from the circadian rhythm that we talked about to all of these wonderfully long words that most of us only attempt to think about after enough caffeine.

But somehow you've still made this feel wildly accessible and empowering. This deep dive into hormones and how it shapes our, not only our brain health, but our health health across a lifespan.

is just such a gift and I'm so delighted for the clarity, nuance, and renewed appreciation that I have personally for hormones and their complexity when it comes to protecting cognitive health.

So everyone, thank you for listening. I hope that this conversation leaves you feeling informed rather than intimidated and curious and not overwhelmed.

Well, it is challenging, but let's put it this way. No hormones is the worst option. Yes, and it might be complicated, but as you reminded us, Dr. Gersh, understanding them gives us a roadmap for healthy aging, for thinking well and aging well.

And so, as, you consider this and talk to your providers about this, I hope that you can refer back to this conversation and use the wisdom and clinical insight that Dr Gersch has so generously shared with us today so passionately.

So it has been an absolute pleasure. It always is when I get to see you and catch up with you. Thank you so much for being here, Dr. Gersh. To stay connected, get bonus resources, and never miss an episode, head over to drheathersanderson.com and join my email list.

Until next time, keep thinking well and aging on purpose.