Hormones, Pregnancy, and Uterine Growth

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 a weed and he's really thin and then he stops growing all these muscles to fill up.

Podcast Introduction and Guest Background

He gets old, he fills out. That's the uterine lining. It grows and grows and then it blossom. 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, you know, 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, Dr. Felice Gersh. She is a word-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. Gursh is one of those rare clinicians who can take complex endocrinology, gut physiology, circadian biology, and brain science and translate all of this into practical, empowering guidance.

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

She's 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 conversation has radically changed.

with social media, some of the celebrity doctors that are out there on social media, some of the 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 last 25 years, right? Including the Women's Health Initiative study. But can you just kind of take us through the landscape of the science, the media, 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.

The Women's Health Initiative and Hormone History

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. So back in the day, I was there when hormones were really growing in popularity.

I was going 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 can, you know, use words different ways.

And it was 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 Madroxyprogesterone.

So that's 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. But by the time that was already in the works, I had already switched to micronized progesterone and transdermal estradiol.

Estradiol is the estrogen made by the ovaries. and conjugated equine estrogens are estrogens 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 equiline estrogens are unique to horses and pregnant horses never to be seen in a human female ever and they 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're 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 estrone is good when you have the right amount and the right balance of other 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, and endocrine disruptor is something that interferes in one of myriad ways with the normal production, distribution, receptor binding, distribution, I think I mentioned that, elimination, detoxification of the hormone, okay?

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

Like, duh, you know, we already knew what they did. You were just saying this in your clinical practice. You had a sense that 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 they were not ideal. They were not ideal.

They could suppress night sweats and hot flashes, but in terms of global health effects, they were not 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. I pleaded with them. I said, 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's not about the uterus, it's not about periods, it's about ovarian aging and the ovarian 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 don't have periods because I had a hysterectomy. It's like, yeah, it's not about your uterus, whether you do or don't have a uterus, it's about your ovaries aging and the loss, you know, the sort of up and down during the perimenopause 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 half did not. It was very personal to me because I was their clinician in the, you know, the cavalry trying to rescue my troops, you know, 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 of 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'm seeing other people use it.

So that's fine. It's like up for grabs. I didn't patent it. And it's 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. And it's like, hmm, I don't think we studied organic strawberries.

So it's like, if you think of the human hormones as the organic strawberries, of course, and then the 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 of women are in menopause. A lot of women are perimenopause. 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?

Like this is, I don't want just antidepressants. No, right, because that's what really happened is that each symptom, because as you mentioned when you were 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 life because they maintain 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, I mean, this is kind of a strong word, but I really do abhor a lot of what is happening in the menopausal sphere.

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

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

Menopause Awareness and the Need for Treatment

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

So I think that they've done a good job of, like, like 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 forever or forever feminine. That was in 1966. We didn't know everything about receptors. 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 that by giving hormones, you had a reprieve. You did better in every which way. stayed more feminine, 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 cows' ovaries and ground them up. Just like if you've heard of desiccated thyroid, you know, they grind up a pig's thyroid gland and put it in a pill, you know?

Well, they did that with cows' ovaries, and then they did cows' placentas. and then they did horse urine, and the horse urine, Premarin, which Premarin, P-R-E, for Pregnant, and Mararin for Mare, and then in, well Mare for for mayor and in for your in.

Clever marketing. Premarin, right? So that came out on the market. It was FDA approved, I believe in 1942, okay? So that predates me, by the way. I wasn't there for that one.

But the bottom line is that 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.

It doesn't mean they're great. Think of earthquakes, tornadoes. Yeah, they're natural, but get out of the way if you can. But we can't get out of the way of menopause.

It's universal. It doesn't matter what ethnicity, what continent, what social strata you're in. If you're a female, you live long enough, you will go into menopause.

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

eggs.

It's like a cause and effect. That's a clear cause and 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. There's a generation of women who was basically denied hormone therapy after they went through menopause and they suffered.

Their relationships suffered, their families suffered, their health suffered. I mean, they really have… Their lives they did 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 was like ridiculed, oh my gosh, what that guy must've gone through with the way he was treated in the, in the journals and everything else.

But he was an academic and he was like more out there than me. Cause I was like in my office in Irvine seeing patients, you know, raising four kids. I wasn't out there, you know, and.

was just trying to do the right thing and I read like crazy, I 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 menopause 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 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's 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, they'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 menopause and they're 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 40s, you should go on 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're talking about depression, mood changes, there's so much more than, like you said, that just the hot flashes and night sweats.

Well, I would love love to go over, I hope that we'll have time to go over, like sort of just sort of wrap up the history and the last 10 years and then really go into like 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 sort 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 menopause. 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.

It's like, how about 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.

Birth Control, Progesterone, and Brain Effects

But what's happened, which is very good, as I was saying, is that the issues surrounding menopause, the harms of menopause 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 lot of people know there's problems with menopause for every organ system, or at least they know a little bit more, or it's variable, but definitely more than say, 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 not always getting the word more and more at the medical societies.

They're educating more and more. And I do that as well, 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 of 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.

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 a 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, like those of us who were there, you know, and like I mentioned Dr.

Sorrell, like he put out a paper talking about all the unnecessary deaths like you talked about all 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 lost generation of women you know and he talked about that and how many lives were lost using some kind of um you know 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 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. So women not only have had poor quality of lives, like you said, and 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's 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 it because there's still many people that don't know the nitty gritty of what really happens when you lose these hormones.

But there's more and more people talking about it, 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. And so there's been a lot of entrepreneurship in the menopause world and involving hormone, do I call them hormone distributors?

You know, they are, a lot of them are online, not all. Well, I don't want to name names, but there's a bunch of them out there. And then some people also have offices, but there's a lot.

And their goal is to obviously make money and also hopefully, I mean, because I don't know them personally, hopefully to do some good. You know, 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, a little bit of that.

That is not the way the female body works. And so we are you know, everyone now understands that there are rhythms, like everyone's heard of, like you mentioned earlier, the circadian rhythm.

That's based on the 24-hour rotation of Earth on its axis. It's, like, fascinating. There are creatures on Earth, like humans, who are diurnal. We're most metabolically active in, you know, burning energy and doing all kinds of activities with our brain that are focused, cognitively aware, and we're awake during the day.

That's diurnal. Then you have nocturnal creatures like owls and rodents. They do most of their activity and they're awake at night. 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.

And it's not an accident, 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's so amazing that we are basically truly, okay, 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 genes in our bodies are related or are clock genes.

That's how much we live on a timer, okay? And when you have 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 don't have to know how to do an exam. You don't have to know about anything really much.

You just have to memorize a few protocols and a few what ifs, a few, 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. And when you take progesterone orally, the history of progesterone is interesting. They couldn't make progesterone initially, just like they couldn't make estradiol, so they had to come up with a fake one that they could manufacture, and they came up with what became a made-up word called progestins.

That's what they put in birth control pills, progestins. In fact, birth control pills work because of the progestins, 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 and pregnancy. It's all from the fake, we'll call it fake progesterone.

Progesterone is a single type of molecule. in a family that they sometimes call progestagens, which includes the fake ones, the progestins, and the real one, progesterone, they call them progestagens.

So the fake 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 estradiol 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.

And that sort of became a thought process that you could just do that even for hormone therapy in menopause. So 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. And I mentioned the history of progesterone. Finally, they were able to manufacture progesterone.

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 progesterone that allowed it to get through the digestive tract without being broken down into its component amino acids.

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 progesterone gets into the liver? 80% of it is converted into other stuff. The other stuff is called metabolites.

The main other stuff, the main metabolite, is a molecule that is not progesterone, but it comes from progesterone, which is called allopregnanolone. Now, you also get some progesterone 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 when she makes it, is 10 up into the upper Okay.

Now what levels do you get from oral progesterone? Like two, typically, I mean, 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. And progesterone is very important. Like we'll talk about, like progesterone 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. That's all they think about it.

That's why they say, if you don't have a uterus, you don't need progesterone. I just wrote an article, hopefully will get published, on why every woman with or without a uterus needs progesterone.

But she doesn't just need progesterone. She needs it at the right amount. Everything is dose dependent, right? 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. 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 hormone therapy. And part of what they described was that women when you added progesterone, you reduced the risk reduction.

So basically, you reduced the benefits. And so if you could use estrogen without progesterone, that that would be more beneficial. What I hear you saying is that, no, we need progesterone, 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 like an exhaustive study of everything that everybody's prescribed, but generally they get a very tiny dose of estradiol transdermally.

Like they'll start with the patch dose of like the lowest dose, 0.025 milligrams. So 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. You hardly can measure any change. That doesn't mean that people don't feel a little better or that it doesn't 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's different than placebo because placebo effect is 50%. And then they give that little dose, usually 100 milligrams, occasionally 200 of progesterone.

Hormones, Brain Health, and Late-Life Therapy

And here's the problem with that. So there's a number of problems with these routines of regimens. When you give oral progesterone, like I mentioned, you get very little progesterone, but you get a lot of other stuff, the metabolites, the dominant one being allopregnenolone.

So allopregnenolone 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's called a neurosteroid, because it's in the brain.

And progesterone is a neurosteroid too. It's also made in the brain, but not anywhere in enough quantity in menopausal women to do what it needs to do.

So allopregnanolone in the right amount at the 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. GABA 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 GABA-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.

You know, that's not 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.

So, Too much of a good thing is a bad thing. So there's rat data, you know, of course there's 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 long-term data on dementia, but we do have data showing it can impair memory formation.

oops, that's not so great. So those are problems. So if you 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 progesterone. 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 regimen. And the other problem is that progesterone, and this is actually why they give progesterone every night a little bit, because there is so much fear of bleeding.

I'm a gynecologist. I'm not afraid of the uterus. It's like my friend. I understand the uterus. I understand scheduled 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 normal menstrual cycle, the first part, you only have estradiol and the amount starts very low, day one of a menstrual cycle is the first day of the period, the estradiol is very low, it's in menopausal range usually, and then it comes up, and then you get this spike of estradiol, and that triggers a spike of luteinizing hormone, and that causes ovulation, okay?

Now, 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 second half of the menstrual cycle, estradiol 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 the 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 lot of progesterone, a lot more progesterone than estradiol.

But the amount of estradiol 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 allopregnanolone is used to treat postpartum 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 substances. They're treated by the DEA, Drug Administration, and enforcement. They are treated the same way and they're kept track of.

You know, you have the special prescribing type of thing for controlled substances like Valium or Xanax. You know, 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? Oh my goodness. 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 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 progesterone because they misuse that word all the time when they're talking about progestin, madroxyprogesterone acetate.

Madroxyprogesterone acetate in the brain and in the 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. The women who were not on real progesterone, they were on anti-progesterone.

Of course, they did worse. Now, here's the other thing about real progesterone. The way that it works, and the reason I brought up the menstrual cycle, is that when you make progesterone in the menstrual cycle, all progesterone, it down-regulates the action of one of the estrogen receptors that's called alpha.

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 factors cause 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 in order to maintain a healthy female to create new life multiple times, you have to have functioning healthy organs everywhere all over the body.

That's why these hormones are 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 to have unlimited babies at all, but it's important to understand 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 made by action of an enzyme called nitric oxide 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 the menstrual cycle is called secretory. It's like blossoming. The uterine lining blossoms. Think of like a teenage boy. He grows like a weed and he's really thin and 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.

It's a really gentle blend here of growing and stopping growth 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 the 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 progesterone every single day, is to down regulate the growth factor production of estradiol for the uterine lining.

So, because they don't want to have bleeding. They don't want to have bleeding. But here's the problem. Those same growth factors that grow the uterine lining, create growth and maintenance, not just growing, but restoring, rejuvenating, maintaining the brain with these peptides.

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 peptides 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, like vasointestinal peptides, so many peptides, peptides that are involved in mitochondrial function, which estradiol is critical for the 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 estradiol 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 uterine lining, you must shed it. And to that end, we have to have cyclic progesterone so that we create a period. And you have to 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 is 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 unnatural. Every drug is unnatural. Every procedure is unnatural. 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.

And this is like a huge takeaway that I want everyone to hear is that 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, you know, with a whole lymphatic system, which by the way is modulated by estradiol, duh, everything is.

And progesterone is also like critically important. Progesterone is neuroprotective as well. And estradiol is neuroprotective. 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 need more research.

But even without the clinical studies, we have a lot of science, a whole bunch of science. 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 of them are modulated by estradiol. Okay, so if you have enough estradiol, you'll make the right peptides at the right time and they'll work because estradiol also is very important for receptor function.

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

You know, 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're just different and they have different effects on receptors.

Some of them block, you know, like madroxyprogesterone acetate can actually act as a progesterone. blocker. When you take conjugated equine estrogen, aka premarin, you get all these weird horse estrogens, plus you get 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 that Premarin increases the risk of blood clotting 400% above baseline. So that alone could explain it. The same thing with dementia. they could have these little micro strokes, right, from having extra clotting.

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

So there's a lot of reasons why that wouldn't have been like great for older women.

Receptor Function, Inflammation, and Dosing

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 lot of human data. The human data that is, is mostly in vitro, like they'll take arteries out of the body in very unnatural situations. and then they'll infuse them with estradiol and in one infusion and they'll 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 one study where they took out the uterine arteries from women who had hysterectomy. So they have the uterine arteries.

It's hard to say if those uterine 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 body.

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 basal 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't have lots of data. That's like one study using uterine arteries outside the body. And then there's a mixture of data.

There's some that show good response, less good response. So what's the concern anyway? that one of the concerns is that the estrogen receptor alpha, now I mentioned estrogen receptor alpha, there's three estrogen receptors that are in humans, alpha, because we love Greek letters, alpha and beta, and then there's a G protein coupled receptor that works only on cell membranes.

The alpha and beta are primarily, but not exclusively, nuclear receptor activators, so they work in the nucleus of the cell to create different proteins and or peptides and but they also now we know work on the cell membrane to create rapid response so 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 amino acids and that but the The alpha and the beta also work on the cell membrane to have very rapid effects, very rapid effects, and they also interact with one another.

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 another day.

Because pregnancy is a 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, like 2-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, very involved in it.

And then we have 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't have estradiol in the vicinity, it won't bind and the very important actions won't occur.

So estradiol has so many different like side issues and so on. And so all of these are important. And the alpha receptor. is very 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 the hypothalamus of the brain that activates.

temperature and the autonomic nervous system and appetite regulation, energy utilization. So it's very, very, very important. And also related next to it, the hippocampus, which is very important in memory formation.

So alpha is very, very important and, you know, 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're over 60 or they're 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 studies that exist 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. They 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, and 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't use the right hormones or the right dose or anything, but it showed no harm.

So that is a really good one 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 first year only after they started on these hormones, they had a higher rate of heart attacks, belief 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 of a thing. It's like it knocked off the women who were really like on the edge.

And then after that, it seemed to even be beneficial. So it's kind of a weird thing, but that's using PremPro. So 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 you 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 the 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 women who have just 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. Progesterone is highly anti-inflammatory, and estradiol 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 and function of estrogen receptor alpha.

So maybe you can't give estrogen in a vacuum. Maybe it's necessary but not sufficient for anything. You have to include all the lifestyle things. You have to include fitness and stress management and sleep management and nutritional management, avoidance of toxicants, look into chronic infections, all the 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 function of estrogen receptor alpha in clinical practice, not just in some research lab.

You know, not just using rats. You know, how can we actually measure this and then how can we then follow it? You know, you can't monitor what you never measure.

So what kind of substitute can we use to monitor? You know, maybe inflammation markers, maybe looking at vascular dilation, like flow-mediated dilation.

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 give to a menopausal woman or one that has no estradiol, if you give her estradiol, 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 estradiol, the artery dilates. Okay? They've shown that. That's like, but not in 80-year-olds. They didn't take 80-year-olds.

Okay. Then what happens when you add progesterone? This is real data from little study. If you have a certain amount of estradiol and then you add a small amount of progesterone, the artery 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 estradiol, you increase the estradiol to be more similar to alludial phase estradiol.

And in the study, they actually measured estradiol levels. And they actually gave estradiol 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 the luteal phase.

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

Add the estradiol higher, the artery dilates, and then add the progesterone, the artery stays dilated. So this is all about dose and regimen. Dose dependence.

Closing Thoughts on Hormones and Healthy Aging

So I am now looking at moving forward, giving a higher amount of estradiol and a lower amount of estradiol depending on whether the progesterone is being used for the first weeks of the cycle, NOAA progesterone, the second two weeks progesterone, then how about giving the progesterone optimally, not this Oral stuff that that's a micronized oral where you get very little progesterone and remember progesterone Increases nitric oxide, but it's all this this beautiful dynamic because progesterone down regulates the alpha receptor, which is key in nitric oxide Function, okay.

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

And it's all designed not to bleed by giving too little estradiol and then oral progesterone, which gives you too much metabolite like allopurinanolone, which can potentially 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 progesterone so that you don't down-regulate the production of nitric oxide or factors for the 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, it's like in daily same amount, it's just that makes zero sense.

That makes absolutely no sense. That's better than nothing, I hope, from a lot of women. You know what? I always said that. I always said any hormones are better than 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 to 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 why they haven't yet shown that giving hormones in the way that we're giving them, like, prevents dementia. They haven't shown that. Maybe it's because you've given it wrong.

It's not the hormones, it's 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 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 hormone may 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.

Gersh 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. Thank you so much for listening to the Think Well, Age Well podcast. If you enjoyed today's conversation, please take a moment to subscribe, leave a review, and share this episode with someone you care about.

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