

Episode 159 Transcript

00:00:00:02 - 00:00:12:21

Dr. Felice Gersh

These hormones are essential for women to be healthy, and only healthy women will have successful fertility and pregnancies without having all kinds of complications.

00:00:12:22 - 00:00:38:08

Dr. Jaclyn Smeaton

Welcome to the DUTCH podcast, where we dive deep into the science of hormones, wellness and personalized health care. I'm Doctor Jaclyn Smeaton chief medical officer at DUTCH. Join us every Tuesday as we bring you expert insights, cutting edge research, and practical tips to help you take control of your health from the inside out. Whether you're a health care professional or simply looking to optimize your own well-being, we've got you covered.

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Dr. Jaclyn Smeaton

The contents of this podcast are for educational and informational purposes only. This information is not to be interpreted or mistaken for medical advice. Consult your health care provider for medical advice, diagnosis and treatment. Hi and welcome to this week's episode of the DUTCH Podcast. Now we're going to talk today about oral microRNAs, progesterone, which has become the go to progestogen for most of us who are practicing hormone therapy in menopause, and for really good reason.

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Dr. Jaclyn Smeaton

The safety data over synthetic progestin is really solid. Breast cancer risk, cardiovascular outcomes. Venous thromboembolism OMP just looks favorable across the board. But today we're exploring a question that's been coming up in clinical conversations. We've had a lot of you reach out to us with questions about this. And this is one that really doesn't have a clean answer yet.

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Dr. Jaclyn Smeaton

My friend and colleague, Doctor Felice Gersh, has been asking whether chronic nightly OMP use specifically what it does in the brain via its primary metabolite, Allopregnanolone Whether this is something our field has really fully examined, she's not making a definitive claim, and she's totally open that she's drawing on the

combination of animal studies and basic science research.

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Dr. Jaclyn Smeaton

But she does point to some really interesting parallels with what we know about long term benzodiazepine use, which has a similar mechanism of binding in the brain and asks whether we have enough long term human data to be confident that we've answered the question about oral microRNA as progesterone. The spoiler here is we don't. Not yet. So today's episode, where I'm also joined by our founder Mark Newman, isn't about telling you that something new is definitively true or that something you've been doing is wrong.

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Dr. Jaclyn Smeaton

It's really about mapping what we know, being clear on what we don't know, and where the gaps are, including some protocol considerations that you might want to think about when it comes to dosing OMP, maybe cyclically or using vaginal progesterone. And it's really worth understanding all of these in context. If you don't have a lot of background information on this.

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Dr. Jaclyn Smeaton

I also wrote a blog, which goes into some of the research that we're going to be talking about on the podcast today, because I think it will really help you orient to this conversation so that you can click to in the show notes. If you want to have a read before you have a listen and just know that's a resource.

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Dr. Jaclyn Smeaton

If you are listening to the podcast and maybe need to slow it down and get some background information. But ultimately, I want you to think of this as less of a conclusion and more of a well-informed conversation about where the science is and where it still needs to go. And personally, I love these exploratory conversations I found to be so exciting to be a part of because there's so many gaps in research that we're all excited to eventually cross.

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Dr. Jaclyn Smeaton

So let's go ahead and dive in. Doctor Felice Gersh, medical doctor, is a globally

recognized expert on women's hormones, gut microbiome, and circadian rhythm. She was one of the first dual board certified integrative gynecologists in the United States, and she's so passionate about helping patients on their journey to optimal health. She currently serves as an affiliate faculty member at the Fellowship and Integrative Medicine through the University of Arizona School of Medicine.

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Dr. Jaclyn Smeaton

Doctor Gersh is really a born educator, and she's been featured on so many guest podcasts, webinars, medical documentaries, and more. We're really lucky to have her back on the podcast today. Let's go ahead and get started. Well, doctor Gersh, thank you so much for joining us. That's podcast again this week. Thank you so much and Mark for joining us as well.

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Dr. Jaclyn Smeaton

It's always nice to have you jump into the conversation. So today is going to be a great one.

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Dr. Felice Gersh

Well I'm really excited to be joining you. And the topic that we're going to talk about. We were talking Mark and I before. It's like really important. And so I'm really excited to have this opportunity to discuss this with you both.

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Dr. Jaclyn Smeaton

Fabulous. I mean, we're going to be talking today about progesterone, and I'm really excited to dive into this because I've kind of heard through the grapevine from people who've heard you speak at conferences, and I want to dive into all of this new kind of new research that you've been sharing and your your thoughts around progesterone use post-menopausal.

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Dr. Jaclyn Smeaton

But before we do, just in case there's anyone on the planet who doesn't know who you are, which I think is tough at this point in our world at least. I do love hearing a little bit more about your background, and I just find it so fascinating because you're trained in board certified in both about time as well as integrative medicine.

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Dr. Jaclyn Smeaton

And that's a fairly rare combination, I think. Can you share a little bit about like how you came to bridge those two worlds, and what do you think that dual lens really offers to patients?

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Dr. Felice Gersh

Well, it's hard for me to even know why. It just became sort of ingrained into me that there was more to offer to patients than I learned in my medical school and residency training so early, early on in my practice. And I started my own practice from scratch. I brought on board what I called my ancillary team, so I incorporated very early in my practice.

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Dr. Felice Gersh

So decades ago, a Chinese medicine practitioner, massage therapist, biofeedback psychologist, nutritionist, massage therapist. So I didn't even really think I was like, really ahead of the curve. It just seemed like all of these things were necessary. In addition to my conventional therapy, my my conventional therapeutic approaches. Well, what happened was about 25 years ago, I started thinking, well, maybe I should have some training.

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Dr. Felice Gersh

Well, I didn't really get to it until I finally gave up doing obstetrics because I was busy delivering all those thousands of babies. And after I stopped doing obstetrics. And now this is going back quite a few years ago, over 15 years ago, I felt this real void in my career. Like I didn't know what my purpose was.

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Dr. Felice Gersh

I did a lot of surgery. I taught how to do gynecological surgery, but I thought, this is end stage disease. Can we be a little bit more proactive here? Do we have to wait and say, let's wait and watch? And then when it gets really, really bad, we'll cut organs out? It seemed like we needed to be more proactive, but I didn't really have the tools.

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Dr. Felice Gersh

I had my my ancillary practitioners, but I didn't have any of that training. So I went on a journey. I started going to conferences with naturopaths, with chiropractors, functional medicine doctors. But I was kind of doing a random sort of my own guide, and I didn't really have a real plan. And then at one conference, I was the only MD, and I was in a room filled with other naturopaths, and I went up to Doctor Loa dog.

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Dr. Felice Gersh

And I said to her, I'm really lost. I really feel like I don't have enough opportunities and knowledge to actually help my patients to optimize their health and to be proactive. And she said, well, why don't you come to the fellowship in integrative medicine? A new session is starting very soon, and I know you're qualified. So I went home that Friday, rather Sunday, and I filled out the application.

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Dr. Felice Gersh

Two weeks later, I was in Tucson. I did the two year fellowship in integrative medicine at the University of Arizona School of Medicine, and I finished way back in 2012, and then it became a board certified program. It became board certification, as an option, which is like just like if you're board certified in internal medicine or interventional radiology is like a real official board.

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Dr. Felice Gersh

And I was I think I can prove it at this moment, the first ObGyn in the world who actually became dual board certified in both ob gyn and in the new field of integrative medicine. And then I've never looked back. I just keep moving forward and taking more courses. And now I teach courses, you know, so it's like that's the evolution.

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Dr. Felice Gersh

And so I love what I do. And that's why I love associating with other like minded sort of, you know, people who question the status quo and are always looking for answers like you guys.

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Dr. Jaclyn Smeaton

We certainly love that. And you're a gem to have as a mentor in a, in a field that's

continually growing. You know, I think there's it's really interesting that lately you're hearing more, particularly OB GYNs come out and say things like, I only got 30 minutes of menopause training or one hour of menopause training or 30 minutes of nutrition, and my whole med school program.

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Dr. Jaclyn Smeaton

And I think for people that have a natural curiosity about the why that underlies disease, hearing your trusted health care providers that are conventionally trained share things like they only got an hour on menopause education. You know, it's it's remarkable. And it could just goes to show you how that continual education is just so critical. If you want to find a provider who's really knowledgeable, to be able to help you in the way that you're looking for.

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Dr. Felice Gersh

Well, sometimes being around for a long time can be good. And I'm one of what is relatively a small percentage of practicing OB GYNs who actually were around when the Women's Health Initiative was published back, you know, around 2002 and three and, you know, when it was all coming out. So I was practicing medicine prior to that. So I actually did have education, and I had a lot of experience prescribing hormones before and then ongoing after the Women's Health Initiative.

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Dr. Felice Gersh

Well, I will say catastrophe. And so I do have that I'll say earlier wisdom, an understanding of hormones. And now they're talking about at least 80% of current health care practitioners across all the prescribing areas of medicine, over 80% of them were not practicing medicine back in the early 2000. So they once that happened, that Women's Health Initiative came out.

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Dr. Felice Gersh

That's when education and research came pretty close to a grinding halt. And even the studies that were done were based on the philosophy of the Women's Health Initiative, which was hormones are risky, hormones are dangerous. If you use them at all, go with the smallest dose for the shortest period of time. And that way of thinking, that mantra pervaded even additional studies to few ones that came out afterwards, which they even put into their studies.

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Dr. Felice Gersh

You know, we actually used that philosophy. And so I talk over and over about whenever you're giving something, whatever it is, do you want the lowest do you want the highest or do you want the best? You know, I say, I think we want the best. So lowest only makes sense when you're dealing with something that's toxic. It's like if I said to you, well, how much murky would you like in your diet today?

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Dr. Felice Gersh

I think you'd say nonetheless, you know. So why would we want lowest? We want best. So that's where it comes in. Like what is best. And that's been my journey in that arena of hormones is I want the best and that's where it's been questionable. What is best best in terms of dosing. Best in terms of cycling, best in terms of how to give the hormones.

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Dr. Felice Gersh

Because I've always known that menopause is a huge metabolic hit to women's health, you know? So that always was clear to me. So wasn't a discovery that menopause matters. It was what do we do about it? And that's still the prevailing question in my mind. It's like, okay, menopause is a condition of hormone insufficiency and then into deficiency.

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Dr. Felice Gersh

So what are we going to do about it? And that's to me the overriding question.

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Dr. Jaclyn Smeaton

Well, I'm excited to spend some time talking today about this very thing. And particularly for postmenopausal females. We're talking so much about, how we should be doing the best hormone prescribing for patients and marked something that you've been really passionate about as well. And I want to just frame up the conversation because we talk a lot about estrogen when it comes to menopausal hormone therapy.

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Dr. Jaclyn Smeaton

And then we talk about progesterone kind of as the necessary sister for women who have a uterus. This is kind of the conventional trope. However, there's rising knowledge around the importance of progesterone in cycling females and then even in pairing postmenopausal females. So I want to start by just laying the groundwork for people who might be newer to hormone therapy providers, who might have been taught you only need progesterone if a woman has a uterus, and the only purpose is endometrial protection.

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Dr. Jaclyn Smeaton

All right. Let's just start with that. What would you say to someone coming in that has that point of view? Because that's how they've been trained.

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Dr. Felice Gersh

That is the pervasive attitude. In fact, all the medical societies currently recommend no progesterone prescriptive use at all in women who don't have a uterus after a hysterectomy. They say don't prescribe progesterone. So I say that is misguided thinking. Okay, pure and simple. There is no one thing in the body that does one thing in the body. Okay?

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Dr. Felice Gersh

So every peptide, every enzyme, every neurotransmitter, every hormone has multiple effects in multiple organ systems. It's not a one hit wonder that only works in one spot. And it's absurd to think that progesterone is only about endometrial protection in menopausal women. There are receptors in many, many organs throughout the body, and the ones that have had the most research are the neurological system, the the bones, the immune system, skin vascular system, the cardiovascular system.

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Dr. Felice Gersh

So we know that there are multiple a multitude of effects that progesterone has throughout the body. Now, one of the things I always emphasize is that these hormones that have traditionally been called sex hormones, estradiol and progesterone, will leave testosterone out of it for now. But estradiol and progesterone have classically been referred to as sex hormones, so I refuse to call them that.

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Dr. Felice Gersh

I stopped a long time ago, and I call them life hormones because they are the givers of new life, and they are also the providers of a healthy life. And that is so important to grasp that these hormones are essential for women to be healthy. And only healthy women will have successful fertility and pregnancies without having all kinds of complications.

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Dr. Felice Gersh

This became obvious to me early on in my career, when I was delivering those thousands of babies that women who went into pregnancy, whether by luck or through artificial means, and they got pregnant if they were unhealthy, metabolically speaking, at the time they entered into pregnancy, they were a high risk for having pre-eclampsia, gestational hypertension, gestational diabetes, preterm labor, and so on.

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Dr. Felice Gersh

And so to that end, these life hormones estradiol and progesterone have effects throughout the body to maintain health because without having total global health, a woman will not be successful with pregnancy. If you understand that the Prime directive of life is the creation of new life and only humans, the only species on planet Earth that works to control our own reproductive destiny.

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Dr. Felice Gersh

There's no animal on planet Earth that says, hey, this is not a good year to mate. It doesn't work that way. But it's. And I'm all for I'm like the ultimate feminist here. So I'm totally for women to have babies or not have babies when and if they want them. But if you don't understand the foundational evolution of the female body that it's designed for a successful reproduction, and to that end, you have to have optimal hormones from the ovary in order to optimize the health of every organ system.

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Dr. Felice Gersh

So I am a strong advocate for giving progesterone in a physiologic way to optimize the effects of progesterone on all the different organ systems that require it for optimal

function. And that includes after a hysterectomy in fact, that's what I'm doing now. I just wrote an article I hope will be published on why every woman who's had a hysterectomy needs to continue to use progesterone for cardiovascular optimization.

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Dr. Felice Gersh

But then I want to write one for bone, for brain, for skin and for, you know, and so on, because that's how it works in conventional medicine. You have to pick an organ system to get into a journal that specializes in that organ system. But it's the total body unified approach to health that these hormones have receptors all over the body.

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Dr. Felice Gersh

People now understanding estradiol, that it has receptors in all these different organ systems. So let's get on the ball. Progesterone is also about global health and functioning of multiple organ systems.

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Dr. Jaclyn Smeaton

Well I you are in good company with that belief system I think here before we get into those details, which I do want to get into, like what do we know about progesterone for all these different systems of the body, for post-menopausal women? Mark, I'm hoping that you can kind of lay the groundwork for us from the biochemistry perspective, particularly around progesterone metabolites, which is something that we measure at Dodge.

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Dr. Jaclyn Smeaton

And we care a lot about it because progesterone metabolites actually have their own biological, impact, which we are going to be talking about today in depth. So, Mark, can you explain to us a little bit about the biochemistry behind progesterone? And then I also I'm hoping you can talk a bit about progestin versus progesterone, because I think that's something from the why, where there were some risks associated with progestin use that would be really helpful to clear up from a risk data perspective and why what we're talking about today is something a little bit different.

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Mark Newman

Yeah, maybe starting with that aspect of it is I mean, just to keep it as simple as possible, different chemicals, you know, that have different impacts on the body. And I mean, we always talk about how frustrating it is to read papers where they interchange them, even to have the word progesterone in the title. And then as you get to page four, you're like, oh, you I get into the methodology and you're not talking about progesterone, you're talking about a progestin.

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Mark Newman

So, you know, the body makes progesterone. And in a certain respect it works. Also to use a synthetic version of that. And so in the study and in many practices, they reach for that. And there are reasons for that, that might get into politics and all of that, which I will not get into. Just to say they're different compounds and different chemicals.

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Mark Newman

And, you know, the benefits of natural progesterone aren't completely mimicked by the synthetic progestin, although they do protect the uterus from, too much proliferation when you also have estrogen on board. So a lot of confusion over that over the years. And we could get more into that. But as far as the metabolites go, that's a unique window that we have.

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Mark Newman

In a certain respect, the metabolites have a very simple role, and that is that progesterone itself doesn't really end up in urine. And very significant concentrations because of the uniqueness of its structure that is uniquely different than testosterone and estradiol and some of the other compounds. And so there's there's a fair amount of research that shows that, the these metabolites called preg, named, I'll track really well with serum progesterone, with whole body progesterone as progesterone moves these metabolites move, there's one main pathway of, the beta pregnancy dial.

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Mark Newman

And there's decades of research on how that tracks pretty well with progesterone. What we did that was unique is knew that a decent fraction of progesterone also went down this other pathway, down this alpha pathway. That also has a similar purpose in that it tracks with progesterone. So progesterone is, you know, in a sense, going down

two pathways and creating these two sort of cousins, if you will, of metabolites, both of which track with serum progesterone, track with whole body progesterone when you're not in HRT land.

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Mark Newman

And so we measure them both and they correlate and we've published that and that's great. And so that's one use of metabolites is just a window into how much progesterone did Jaclyn make today or whomever it might be. And then you start to get into unique the progesterone unique biochemistry of how it's broken down. And then the metabolites take on a whole nother purpose, which admittedly has less value and less utility in just knowing how much progesterone you make.

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Mark Newman

But it also is interesting and in certain applications has some, some clinical value in and of itself in asking the question, what is my body doing with progesterone? And so these, these alpha metabolites, very much like when or when testosterone goes down its alpha pathway, it makes its famous metabolite, DHT, which has a lot of interesting use.

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Mark Newman

And we don't need to get into that. But progesterone, in the same way, when it goes down that alpha pathway, those metabolites have some, unique properties, some of which is they're sedating and hit the gabber receptor. And there's a whole story, you know, there with, with that. And that's, I think, a good lead in. I can just sort of maybe leave it right there.

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Mark Newman

In the sense of, the big story being there are two uses of one, it's indirect way of saying how much progesterone you make, and then two, we get to dabble a bit in, in understanding how your individual progesterone is metabolized and why that's interesting. And then that gets a little more interesting when you start ingesting progesterone, because those metabolism profiles and pictures are different from woman to woman, but they're also very different depending on whether you're swallowing progesterone, taking it in vaginally or, you know, by other, routes of administration.

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Mark Newman

So it's, it's a multilayered interesting topic.

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Dr. Jaclyn Smeaton

Yeah, it certainly is. And just saying and I think, you know, this is an area that's so commonly confusing for even providers. Let alone for patients. But when we look at like birth control pills, most of them are there's synthetic hormones, ethanol or diol plus some kind of progestin. And there's a lot of different progestin available on the market.

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Dr. Jaclyn Smeaton

There's no rush syndrome and lever and are just all Das adjustable. Despair unknown. I mean, we could see progesterone acetate, like all of these ones that are utilized in cycling females. And then you have the studies that were utilized, with the GI, which are using, again, a synthetic progestin. I think most providers now that I've seen at least are using a bioidentical progesterone and estradiol approach post-menopausal, although it's not off the table to use other synthetic progestin in certain cases.

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Dr. Jaclyn Smeaton

But there's obviously a big difference between those. And I think providers really get that, you know, not all progesterone or progestin are created equal, and only the natural bioidentical progesterone can make these metabolites. That can really have all these profound effects downstream. Right. So, Doctor Urs, can you talk through a little bit about let's focus in on the bioidentical progesterone.

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Dr. Jaclyn Smeaton

Now when we're looking at use of, progesterone products, post-menopausal, the majority are using or a microRNA is progesterone. But there are other forms that are available in the market as well. Can you just lay the groundwork on like what else is commonly prescribed?

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Dr. Felice Gersh

Well, what's interesting about the micronization of progesterone, if we just go back a little historically, is that if someone swallowed progesterone that didn't go through this process called mechanization, the stomach acid would just break it down into amino acid. So it would be of no value at all. It would be very poorly absorbed. But through this process of my quantization, it can survive the stomach acid.

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Dr. Felice Gersh

But then it ends up in the liver. Okay. And the liver is the master organ of we'll call it metabolic transformation. It converts one thing through to another thing through these different pathways that exist in the liver as part of the sort of detoxification. That's the function of the liver, among many others. And so when you swallow microRNAs, progesterone, it survives the stomach, but it ends up heavily converted to metabolites.

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Dr. Felice Gersh

Yeah, we know that we're touched on these metabolites that are produced in very large measure resulting in very, very low levels of progesterone that actually get into the circulation. And large amounts of these metabolites of, you know, over 30 different types. And one of the dominant types of metabolites is called Alo, pregnant alone. And so Alo pregnant alone becomes produced in very large measure by the liver and gets into the circulation and alo pregnant alone in the right amounts or is really a wonderful molecule.

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Dr. Felice Gersh

It's not progesterone, though. It doesn't bind to the progesterone receptors, but it does work in the brain. When it gets into the brain, as was mentioned. So it can activate the Gabba A receptor. And Gaba is the inhibitory neurotransmitter, which is very important for having tranquility and it reduces anxiety. It's good for a mood and it facilitates sleep.

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Dr. Felice Gersh

And it balances other neurotransmitters like glutamate. So it's like part of the whole balancing system. But like anything, too much of a good thing can be a bad thing. So I did a deep dive into like what happens when you swallow all of this progesterone, this

microRNAs, progesterone. And it turns out that in different women, like the said mark was saying it can be variable, but up to like 90% of the progesterone that's swallowed is converted into metabolites largely alo pregnant alone.

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Dr. Felice Gersh

And it really over it can over activate the gab a receptor and they've done some level testing. And when you take 100mg every night, which is so standard nowadays, and we can talk about even forgetting the part about the low pregnant alone and the other metabolite. Why taking having progesterone every single day is not physically physiologically compatible with optimal health, but just talking about the metabolites with the high levels of Alo pregnant alone, it's like too much sedation can occur in the brain and there's a lot of rat data.

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Dr. Felice Gersh

I know it's rad. It's what we call preclinical data. When you do studies in other animals that are not humans, there's even a little bit of human data there that can impair memory formation. Also, in rats, if there's continuously higher levels of Alo pregnant alone, it can alter the appetite regulation systems and actually promote weight gain. And there's a number of studies in rats showing appetite dysregulation and weight gain when they were exposed to abnormal supra physiologic amounts of Alo pregnant alone on a daily basis.

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Dr. Felice Gersh

When someone swallows 100mg approximately two and a half times the maximum amount of Alo pregnant alone in the blood that would ever be achieved during a normal menstrual cycle is occurring, and 200 would get you approximately five times the maximum amount that a female would ever naturally have in her bloodstream. And of course, it goes everywhere in the body, including in to the brain.

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Dr. Felice Gersh

And there it gets even more complicated than that, in that the liver has another enzyme that's much more prevalent in the liver than in the brain, because the brain has the enzymes that can convert progesterone in the brain as needed into Ella pregnant alone. Because it does have these very important effects in the brain. But when you have such a huge amount going into the liver directly, there's another

enzyme system that can actually produce more than you'd ever have in the brain of sort of like the cousin, you might call it a cousin.

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Dr. Felice Gersh

It's like a different configuration in space, which is called ISO pregnant and alone instead of alo pregnant alone. And it acts as kind of a blocker of Alo pregnant alone. So it's actually even more complicated. And the liver is just not naturally supposed to get this bolus of oral progesterone and then have all these metabolites circulating in unnatural non physiologic amounts.

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Dr. Felice Gersh

So what other options are there? Well there's just so many. There's not that many. But you can use compounded pharmacy products to use as vaginal suppositories. You can actually use the same conventional progesterone little like sort of like a little pillow. It's kind of a little bit soft. And they come in white or orange. I usually tell my patients that we could get the white ones if they don't want orange, okay.

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Dr. Felice Gersh

Because it does have that orange dye and it's actually designed. And there's plenty of studies published studies that you can use that same little oral use as vaginal use. So in the infertility world, vaginal progesterone is what is used. They can do shots. But no menopause is going to do shots. It's like not not feasible to do a lot of progesterone shots.

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Dr. Felice Gersh

It's also extremely painful. Even the fertility gods rarely use that.

00:30:33:00 - 00:30:33:22

Mark Newman

00:30:34:00 - 00:31:10:05

Dr. Felice Gersh

Yeah. So anyway, I'm a big advocate now for vaginal progesterone. Whether it's a compounded product or the commercial product, which has plenty of supportive data

that when you use it vaginally, you get what's called the first pass through the uterine cavity, which actually causes the uterine lining to become completely transformed into a secretory state. Like the perfect state for implantation of an embryo or the perfect period, or, and as well, if you give enough, you're going to get good systemic levels.

00:31:10:05 - 00:31:36:08

Dr. Felice Gersh

So you get the benefit to the uterine lining, and you can get blood levels that are more compatible with the levels that a woman would have in a natural cycle, which you will not likely achieve with the oral. Now every there's variations, but even when you do achieve good levels orally, which doesn't happen, typically you're going to get still a lot of those metabolites that we don't want so much.

00:31:36:10 - 00:31:41:00

Dr. Felice Gersh

You know, once again, too much of a good thing becomes a bad thing.

00:31:41:02 - 00:31:52:06

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00:32:24:14 - 00:32:43:21

Dr. Jaclyn Smeaton

Because your position on this, like you said like it's there's rat data and this is how

medicine progresses, right? You start with animal research. You see what you're observing. It moves on to clinical trials in humans. And then there are larger, you know, you go to pilot study, then you go to a larger study, and then you're able to draw better clinical conclusions.

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Dr. Jaclyn Smeaton

And I mean, that process fundamentally takes a very long time, like when we look at the research process and things, making it into standard practice guidelines. But I know that there's also pushback around that point of view as well due to like particularly the keeps trial, which was a trial looking at the safety of oral microRNAs, progesterone, and looking at the fact that it does appear to be safe for most women.

00:33:10:06 - 00:33:25:02

Dr. Jaclyn Smeaton

But I think a lot of it maybe is around the nuances of some of the other effects that you're talking about on the brain, which were not the primary endpoints. You know, did show no cognitive harm in the trial, but what do you say is, I know you've read all this data. What are your thoughts when you look at all of that?

00:33:25:04 - 00:33:55:19

Dr. Felice Gersh

Well, if we talk about the my concern, okay, nothing happens very rapidly. Okay. So this is like the long haul we're talking about in terms of progesterone when you get too much low pregnant a lot I mentioned that there's some data in rats of weight gain and dysregulation of the appetite in rats. They had significant occurrence of what you would call rat dementia because you're suppressing the brain.

00:33:55:19 - 00:34:28:00

Dr. Felice Gersh

You're suppressing memories. Like if you think about what happens when you're falling asleep, you're not making great, brilliant revelations about anything. Your you know, your brain is going into a very like suppressed state. And that's what has to happen in order to fall asleep. So now there is studies on this. If you look at how what what drugs work similarly similar to Alo pregnant alone the metabolite of progesterone, they're the benzodiazepines.

00:34:28:03 - 00:34:59:20

Dr. Felice Gersh

So we're talking about drugs like Valium, Ambien, Xanax. So those drugs work on a different site on the Gabbay receptor. But the same mechanism. It is the same mechanism that increase Gaba. Now, those drugs are scheduled for controlled substances. They're considered potentially addicting and and can impair judgment. And long term use has been studied that it could increase cognitive decline.

00:35:00:02 - 00:35:21:18

Dr. Felice Gersh

And that's what they found in the rats that they had this cognitive decline. But it doesn't happen rapidly. And I'm not going to say it's universal. I would say it's a yellow or red flag saying like, is this okay? And if we have preclinical data that says it's not okay over the long haul, is this what we should be giving?

00:35:21:22 - 00:35:47:14

Dr. Felice Gersh

Plus, when you look at some of the other like negative things, like you're really not getting in most cases adequate progesterone. And once you recognize progesterone has many functions in the body to maintain optimal health, and you're not going to get actual good levels, that's a that's another like concern. So in the keep study, which is just a very few years, I don't think that's enough time.

00:35:47:18 - 00:36:12:00

Dr. Felice Gersh

Yeah. To actually look. Plus they did use it like for only you know, part of the time it was used in a cyclic way, not every single night. Right. Like now it's become the standard of care based not on anything physiologic based on convenience and ease of prescribing, you know, and so on. So I don't think we have the data in humans.

00:36:12:00 - 00:36:38:21

Dr. Felice Gersh

I'm not I'm the first one to be open about that. But when you have warning signs, like there are other studies that have been done for other pharmaceuticals, where there were warning signs in preclinical studies, like using rat data. And so they put, you know, concerns about the drug. I think to do this without having concerns is not right now when when Alo pregnant alone is a drug, you can get it.

00:36:38:21 - 00:37:07:03

Dr. Felice Gersh

It's been used for postpartum depression. And when alo pregnant alone is a

pharmaceutical, which it is a pharmaceutical, it's a scheduled for controlled drug. I think that's really important. When this came on the market as a pharmaceutical, it has the same controlled status as Valium and Xanax and Ambien. It's a controlled substance and it is. It has all the same warnings on the label.

00:37:07:05 - 00:37:38:07

Dr. Felice Gersh

The other thing that has come out once again in preclinical studies, like using mice, where they found that when they gave the mice ongoing levels of Alo pregnant alone that were supra physiologic, okay, that what it did, was it downregulated the receptors so that for progesterone. So it had an impact on how progesterone worked as well when they used progesterone every single day.

00:37:38:11 - 00:38:06:14

Dr. Felice Gersh

And so it could be from the Ella pregnant alone or from the progesterone. It's not like they broke it down. But when they did continuous use of progesterone every day the receptor is downregulated. This is part of the way the body responds when you have something continuously given it down regulates. And then there was concern that when you stop the progesterone that you don't have proper function of the progesterone receptors.

00:38:06:18 - 00:38:44:06

Dr. Felice Gersh

And so that's a concern. So when I have patients who are on nightly progesterone for quite a few years, and then I take them off of it to try them on more physiologic cycling regimens, sometimes they really have trouble sleeping. They didn't have such trouble before. But maybe they're they're Gaba receptors now are completely that's one of the concerns is that when you have constant Gaba activation from constant Alo pregnant alone exposure, that you're down regulating the gabber receptors and creating sort of a resistant state.

00:38:44:06 - 00:39:12:04

Dr. Felice Gersh

And then it becomes very difficult for people to then sleep and have good mood. When you take that away, it's almost like a sort of a dependency or almost like an addiction that only like you don't get a withdrawal effect, like a real addiction, but more like a dependance. So I have concerns of chronic alo pregnant alone effects on the receptor, but also for chronic progesterone use on its receptor.

00:39:12:05 - 00:39:18:06

Dr. Felice Gersh

So, you know, because when you have chronic use you down regulate receptors over time.

00:39:18:08 - 00:39:33:11

Dr. Jaclyn Smeaton

Well, I'm really glad we're talking about this. And this is an area that is an exciting podcast to me, because I think I view our job as bringing information forward to clinicians and listeners. And you feel you the same as an educator. Mark does the same as an educator. And this is one where it's like the jury's not out.

00:39:33:12 - 00:39:49:22

Dr. Jaclyn Smeaton

And I think one thing Mark says all the time, research is really good at telling you what's not true, but it's not so good at telling you what is true. You have to sift through everything. It's not until you have some kind of final conclusion, and we're just in the process with that. And and you and have a history.

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Dr. Jaclyn Smeaton

You and I have had dinner a couple times where I heard the stories from you, of other areas of medicine where you've been you've held the red flag up a little bit earlier than many providers. Pay attention to that. So I really respect the this that you're bringing this forward as a potential concern and issue. I do want to go through just a couple of the studies that we have in this arena, because if people haven't, don't have awareness of it, we've talked about a couple of them already, but just like what they were, what they looked at, what we know.

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Dr. Jaclyn Smeaton

And that. Mark, I want to get your weigh in on this as well, because this is the menopausal hormone therapy is an area that all of us spend a lot of time reading the papers that come out. And, you have a very thoughtful approach as well. So we talked a little bit about the Keats trial. That one.

00:40:35:23 - 00:40:59:13

Dr. Jaclyn Smeaton

I just pulled it up. That was a four year trial. It was cyclic oral micro progesterone, 200mg for 12 days, and then off. So they cycled it like to mimic a menstrual cycle. There were no long term there are no long term studies that I'm aware of on continuous use of oral microRNA as progesterone and cognition. So, Mark, maybe that's the first thing you can share is like what's the difference between continuous and sick.

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Dr. Jaclyn Smeaton

Like what do I mean there. And then the other piece is there has been from a, we could find no randomized controlled trial that looked at continuous use of estrogen and progesterone, I know for more than 24 months. So the keeps did cyclical. The June trial was the one with continuous dosing. But that was only 24 months and only 37 participants.

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Dr. Jaclyn Smeaton

So very small studies and there's really not been long.

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Dr. Felice Gersh

And the elite the elite was also cyclic.

00:41:26:21 - 00:41:41:16

Dr. Jaclyn Smeaton

Thank you. Yeah the elite trial would be the other one. And that one looked at the vaginal gel as well. So we can talk about that as an alternative to. So Mark, tell us a little bit about kind of your unique perspective in this and any thoughts you have to add.

00:41:41:16 - 00:41:44:13

Mark Newman

Yeah. I mean, my thoughts go into like all sorts of.

00:41:44:13 - 00:41:45:02

Dr. Jaclyn Smeaton

I know.

00:41:45:02 - 00:42:12:05

Mark Newman

Just random little crevices of these topics because, and it just goes to show, like how much we have to learn about all of these topics. You know, and, and again, I don't, I don't want to chase down too many esoteric paths. But as we're measuring the metabolites, it's easy to think of it as when you say first pass and you swallow something and eventually it hits your liver as using that to represent the entirety of that process.

00:42:12:06 - 00:42:36:06

Mark Newman

And for me, I like to dig into those little details. There's a 95 paper where they went in and asked, ask like, what's actually going on there? And what they found is that the the bacteria in the intestine actually get the first shot at it. And they said, write down the five beta pathway. And then the intestinal wall is the main one from that paper that sends it down the alpha pathway.

00:42:36:07 - 00:42:53:23

Mark Newman

And then when it hits the liver, the liver goes mostly five beta. And then also these, these esoteric metabolites that have a whole other story that are really interesting of I think it's the three alpha and the 20 alpha. There's an interesting breast cancer, sort of nuance to that. That's never really been, unpacked by research.

00:42:53:23 - 00:43:28:14

Mark Newman

But if the alpha pathway is really interesting, like one of the things that I would like to unpack, but it probably is distracting to this conversation as how you guys are going so far is that the state of the woman's gut? If the state of the woman's gut and the bacteria send it down a pathway, and then the intestinal wall is left to send it down the alpha pathway, which is the one you're talking about, that's a whole area of study that, to my knowledge, has never that's a door that's never even been knocked on, is to say, because what we find in our in our, anecdotes, one at a time, times hundreds and

00:43:28:14 - 00:43:51:21

Mark Newman

thousands of them is you get really different patterns from woman to woman, which I don't think is as much like what's going on in their liver as it is the gut, and what variables actually exist in a woman's gut to really change the metabolic, you know,

state of what she's doing in terms of which, which of those metabolite hormones, that are being made in a particular woman?

00:43:51:23 - 00:44:09:08

Mark Newman

It's just for me. It's a whole area that hasn't been studied that I want to talk about, but then it ends with a bunch of question marks, not with a bunch of assertions. And so, so I don't know how distracting that is, to the conversation, but I think that's a, a really interesting, you know, area of study because the state of your gut matters.

00:44:09:12 - 00:44:42:03

Mark Newman

And then people talk about 100, 200, and 300mg without making, like, really big distinctions. But you're talking about doubling and tripling the dose of this super physiologic, already super physiological progesterone, which has to do also with what dose of estrogen you use. So all this sort of triangulating into a very, very interesting but also potentially confusing conversation with lots of different, lots of different rocks to look under as we as we search for, again, you know, best practices.

00:44:42:05 - 00:45:08:17

Mark Newman

And there's a lot of conjecture in it, and a lot of questions that what you're raising, just like his calling for a lot of research and I and I just, I wish, you know, you fast forward 27 years to see what's unfolded with all of this so that our understanding can be accelerated. And so and it also is a call for a dose of humility with the things that we believe to be true, today, because there is just so much more that needs to be, that needs to be studied.

00:45:08:17 - 00:45:31:19

Mark Newman

And, and at the same point, while we're waiting, we don't want to ignore any of these, you know, whether they're yellow flags or red flags or whatever, that might lead us in a direction, you know, to just treat women better as it releases. So I don't know if I raise more questions that I'm definitely not answering a lot of questions, but that's where my brain goes with that is just in that individuality of women.

00:45:31:21 - 00:45:43:14

Mark Newman

As we're dealing with this and trying to understand that and unpack that more,

because we do see individual patterns that are very strong in one one way or the other. And I want I want to understand more about that.

00:45:43:16 - 00:46:07:14

Dr. Jaclyn Smeaton

So I want to try to steer us one. I think the gut health aspect is so interesting, and we could do a whole another program, so on that, because I think that that progesterone metabolism is a really critical piece to understand. And it's just one more layer as to where you have this connectivity between the gut microbiome and hormonal health, because of course, that's relevant not only for post-menopausal hormone therapy, but also for cycling females.

00:46:07:14 - 00:46:33:01

Dr. Jaclyn Smeaton

Right. It's going to be the same mechanism while you're taking it also potentially not the same depth of impact of the gut microbiome, but certainly an impact there. So I but to kind of keep us steered down the track, I want to talk about a couple things. Just kind of double click on. The first is this aloe pregnant alone exposure from the use of continuous micro progesterone therapy.

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Dr. Jaclyn Smeaton

And I know that there is really when we look at the data one there's not there is definitely that data showing that continuous aloe pregnant alone elevation can impair cognition through the gabay receptor like you talked about. Interestingly, we haven't really touched upon the fact that some studies look at, when we look at cognitive impacts of menopausal hormone therapy, show that intermittent exposure is neuroprotective, and they're actually developing that as, Alzheimer's therapeutic right now.

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Dr. Jaclyn Smeaton

So, can you talk a little bit about what is a difference for clinicians to understand? Yeah. Stick like versus continuous when it comes because I think when we this is very interesting and it's very you know, potentially you're raising a flag of something that keeps ringing. So the next question is like okay, well what do we do about it.

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Dr. Jaclyn Smeaton

And so it seems like we have a couple of options. Let's talk about timing progesterone first. Yeah.

00:47:24:14 - 00:47:50:23

Dr. Felice Gersh

Well when you look at what happens in a normal menstrual cycle, we have a lot of data on that. So there's always like a rationale for all this madness. What happens when you have a dial if you just like a quick review the menstrual cycle has the follicular phase. If we talk about it from the ovarian perspective and proliferative when you talk about it from the uterine perspective.

00:47:51:01 - 00:48:10:23

Dr. Felice Gersh

So the first half, if you have a 28 day classic cycle is the first half is only estradiol. It starts with estradiol being very, very low. The first day of the menstrual cycle is the first day of bleeding, and the estradiol level at that point is very low. Then it starts to rise, but it's still not very high.

00:48:10:23 - 00:48:38:22

Dr. Felice Gersh

Then it goes up much higher and it has a peak that is very high, you know, compared to the rest of the cycle. And then it goes down, and then there's a, an luteinizing LH spike and then a little FSH spike, follicle stimulating hormone spike. And that triggers ovulation. Well, when ovulation occurs you then create what's called the corpus luteum.

00:48:39:00 - 00:49:07:19

Dr. Felice Gersh

And there are these specialized theca cells in it that make progesterone. In order for progesterone to be made, you need to have a dial in an adequate amount. It's a very complex interconnection. We call it the dance of the estradiol and progesterone dance. And during the phase of the first half, which we'll call the, you know, follicular proliferative phase, the estradiol as it's rising, is doing all kinds of things.

00:49:07:19 - 00:49:38:14

Dr. Felice Gersh

It's setting the progesterone receptors. It's creating progesterone receptors. That's essential for progesterone to work. If you don't have proper functioning and develop receptors it the hormone won't work. It's also up regulating testosterone receptors

and its own estrogen receptors as well. So that's a critical time. And all of that will be negated if you have progesterone on the scene at the same time.

00:49:38:19 - 00:50:08:18

Dr. Felice Gersh

Because when you make progesterone in the second half, progesterone actually down regulated to more than one different method. It has an effect in a couple of different ways in terms of the production of the receptor and the function of the receptor of estrogen, particularly the alpha receptor, which is responsible for creating growth factors that grows the uterine lining, which is why they call the first half the proliferative or growing.

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Dr. Felice Gersh

Then, after the progesterone is made, along with very substantial amounts of estradiol, in fact, estradiol levels go up. So the average amount in the second half is higher than in the first half of estradiol. And it's to sort of work in this beautiful coat like project here. Between these two hormones and progesterone is down regulating the creation and the function of estrogen receptors.

00:50:36:12 - 00:51:05:08

Dr. Felice Gersh

And so predominantly the alpha, so that you stop to have a having all that growth. And that's when the uterine lining it like blossoms. And that's when we call it secretory. It's also down regulating the enzyme that creates dihydrotestosterone five alpha reductase. And so it's actually sort of an anti androgen okay. Women tend to have the lowest libido during the luteal phase.

00:51:05:08 - 00:51:26:16

Dr. Felice Gersh

The second half of the menstrual cycle. Which makes sense because they can't get pregnant. And remember it's all about creation of new life. That's the prime directive of life. So nature doesn't care about women having a big sex drive after they can't get pregnant that cycle anymore. So why would we want to create that kind of a scenario by having progesterone on the scene all the time?

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Dr. Felice Gersh

Well, it's not just working in the uterus when you take progesterone, you it's also all

the time, every day, even though the levels are very low, it's not zero. And it's going to affect estrogen receptors everywhere in the body, including in the brain. And when you have all of this progesterone, even though it's low levels but it's constant, okay, then it's going to affect how the brain is going to work.

00:51:52:17 - 00:52:23:11

Dr. Felice Gersh

So you have small amounts of progesterone but enough to suppress estrogen receptors okay. So now it's like a double whammy to the brain because estradiol is critical as in creating new neurons, maintaining neurons, creating growth factors which both estradiol and progesterone can help create brain derived neurotrophic factor, which is critical. Both of them helped to create nitric oxide, which maintains proper vascular health.

00:52:23:11 - 00:52:52:22

Dr. Felice Gersh

And you need to have good blood supply, good nutrients, good oxygen going to the brain. Progesterone in the brain is very anti-inflammatory. It keeps the embedded like immune cells and microglia. The astrocytes, from going wild. It calms things down. It's very anti-inflammatory. And if you think about pregnancy, it's progesterone that helps to work in the interface of the placenta to help prevent the maternal immune system from attacking the embryo.

00:52:52:22 - 00:53:19:20

Dr. Felice Gersh

And this the fetus that's developing through this immune modulation that progesterone does, and it does it in an anti-inflammatory way in the brain to reduce neuroinflammation, which estradiol also works. They worked in synergy. So you need optimal levels for optimal brain health and function. You need to have both the right amount and the right sequence of estradiol and progesterone.

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Dr. Felice Gersh

And once again, we don't want too much ALO pregnant alone. We don't. We need to have activation of GABA. GABA is the neurotransmitter that's predominantly activated by estradiol. It's the same neurotransmitter that's activated by in seven means that are used for people sometimes who have attention deficit disorder issues. They have to give them more focus, more attention, more memory.

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Dr. Felice Gersh

So there's this beautiful balance between these neurotransmitters. So you don't want to be too much playing with that in a bad way so that you have too much inhibitory, not enough activating. You don't want too much of anything and want just right. And when you give hormones like what is now the standard of care, little bitty bits of estradiol too low to actually do enough good, you know, and all this constant but low levels of progesterone and high levels of Ala pregnant alone, it seems like that's the perfect storm for not optimizing brain health.

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Dr. Felice Gersh

But yes, of course we need more studies. But we're working with science. And sometimes that's how expert opinions are created pending more human research.

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Dr. Jaclyn Smeaton

So when we talk about options for prescribers to be thinking about, can you talk a little bit about the continuous versus cyclical dosing of OMP? Is that one good option. And then I know you talked about vaginal and we've got the elite trial that we haven't really dove into. But I want to briefly touch upon that as well as an alternative and just make sure people understand what do we know about that and what do we not know about the use of vaginal progesterone?

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Dr. Felice Gersh

Sure. So when you get back to a normal menstrual cycle, when you have an ending of progesterone, because progesterone would only be present during the luteal phase, which is about two weeks is a little variation, but typically it's 14 days. Well, when the progesterone drops off, that is the ticket to then having its own receptors rebooted and then having estradiol then recreate and activate its own receptors without the progesterone being present.

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Dr. Felice Gersh

And so that's like the whole foundation of what you need to have happen in a normal menstrual cycle. You want to recognize what gives women optimal health. And when they have optimal health, like, say, in their 20s when they would have natural cycles. So we can't actually completely mimic that. It's much too complex, but we can get

somewhere in the neighborhood something way more physiologically aligned with what is optimally going to give optimal health than what we're doing.

00:56:08:03 - 00:56:31:19

Dr. Felice Gersh

So if we give Esther a dial to get levels that are somewhat similar to the levels that a woman would have in a normal menstrual cycle, and there's actually some interesting studies that have been done very small, where they gave a woman who had no estradiol on board, and she had they looked at what's called flow mediated dilation.

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Dr. Felice Gersh

They looked at the artery and it was constricted. Then they added one pill, one patch point one milligram and the artery dilated. Then they gave the woman 200mg of oral progesterone. And they did the flow mediated dilation study and the artery constricted. And they actually measured levels. So the levels were in the 60 to 80 picograms per mil of estradiol with the 1.1mg patch.

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Dr. Felice Gersh

Then another study gave 2.1mg patches to try to be similar to the levels of the luteal phase of the second half of the menstrual cycle. Then they the artery dilated when they gave them the two patches. Then they added 300mg of vaginal progesterone gel once again. So they used the gel and the artery stayed dilated. So end of study.

00:57:26:13 - 00:57:53:00

Dr. Felice Gersh

So what's the conclusion. Well for me it's do both give vaginal progesterone whether it's a tablet or a suppository or gel and give an adequate amount of estradiol similar to what happens in a normal menstrual cycle where when progesterone comes on board, the estradiol production goes up above what it was in the earlier part of the follicular phase.

00:57:53:03 - 00:58:26:15

Dr. Felice Gersh

To have this balance between the estradiol and the progesterone, so that you somewhat suppressed the growth factors, but you don't want to suppress the production of nitric oxide in arteries to maintain vasodilator dilatation. So there's this beautiful balance. So I think that it won't be too complicated to do studies and to do

empirically based on studies that have already been published, to give hormones that are somewhat aligned with what those studies showed.

00:58:26:18 - 00:58:57:15

Dr. Felice Gersh

And they measured levels of estradiol during the both parts of the study. And went with the two patches of 0.1. The levels of estradiol were in, like the 120 to 150 Picograms because we know luteal phase progesterone and estradiol are not at all like like with the follicular and the that women in the second half, the luteal phase, their estradiol levels are typically well over 100 even into the 200 picograms.

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Dr. Felice Gersh

So we're like into that ballpark. And this is we already have data that shows vessel dilatation will be banned or stopped. If you don't have the right ratio or balance between these hormones. So, you know, I think that giving cyclic hormones and accepting I know that some people say it's unnatural. Yeah, but if you want natural it's osteoporosis fractures, you know, hypertension, potential heart attack strokes, etc. all the degenerative disease associated with aging there's natural for you.

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Dr. Felice Gersh

So to continue to have a period that is created artificially through cyclic hormones is a small annoyance. To be dealt with, compared to using hormones in a way that is completely not aligned with physiologic data, that we know that what the way the hormone receptors are not properly aligned and working. When you have this continuous kind of a dosing, you're also not getting adequate levels of estradiol, typically to create adequate growth factors, say, in the brain like brain drive, neurotrophic growth factor, nerve growth factor.

01:00:10:16 - 01:00:44:06

Dr. Felice Gersh

Another thing I didn't mention about progesterone in the brain is that it's really critical for maintaining and producing myelin, the like insulation of nerves. It requires progesterone. So progesterone is neuroprotective. It's actually helped present prevent seizures. There are studies showing infusions after traumatic brain injury can help prevent the degree of damage that can occur without the progesterone. So but nothing happens without the right rhythm and the right dose.

01:00:44:11 - 01:00:49:05

Dr. Felice Gersh

Dose matters and rhythm matters. It's just how females were evolved.

01:00:49:07 - 01:01:15:06

Dr. Jaclyn Smeaton

Yeah. The the study studies on, traumatic brain injury like progesterone, post traumatic brain injury are fascinating to go and do. I want to just review just briefly with the vaginal progesterone options as well? The elite trial did look at 45mg of 90mg of Cronan gel and then also vaginal capsules. But there's really not good long term randomized control trial data with systemic estrogen.

01:01:15:12 - 01:01:37:15

Dr. Jaclyn Smeaton

So I think that's something that we we actually see a lot of providers use vaginal progesterone as an option compared to OMP, oftentimes because oral micro progesterone isn't being tolerated by the patient as well. So I think it's nice, like from my point of view, looking at the data, there is enough data to say that it's I mean, especially what we know about first pass effect in the uterus, the progesterone.

01:01:37:15 - 01:01:41:21

Dr. Jaclyn Smeaton

It's a pregnancy like I feel pretty comfortable with it, but it's not standard.

01:01:41:21 - 01:02:05:22

Dr. Felice Gersh

Of published this published data showing safety for five years because, you know, they don't have long term data on any of this. And there's actually some concern that oral microRNAs, progesterone may not long term be as protective as they think that there's actually been more occasions of endometrial had no carcinoma. So, you know, there's no you're home free with any of these things.

01:02:06:00 - 01:02:38:13

Dr. Felice Gersh

And it's so but you know, when you have regular, predictable bleeding, I can tell you as an ob gyn, that's not how endometrial adenocarcinoma present. It doesn't present with regular, predictable bleeding. That's not how cancers work. So that is actually a signal of good function in the health of your uterine lining. What percentage of women who are on continuous progesterone and daily estradiol, what percentage of

them have some unexpected unscheduled bleeding?

01:02:38:16 - 01:03:02:00

Dr. Felice Gersh

It's really high. It's well over 40%. And in the first year it's well over 60%. In the first six months it's higher than that. So it's not like, oh, if you use the daily routine, you're never going to bleed. Actually, there's a substantial amount of bleeding and because that's unscheduled bleeding, it's always worrisome bleeding because you don't know.

01:03:02:00 - 01:03:02:20

Dr. Felice Gersh

What is that.

01:03:02:20 - 01:03:18:09

Dr. Jaclyn Smeaton

Yeah. And I think sometimes women don't like that because they don't know when the bleeding will happen, when it comes to fitting into their life, where a second regimen, if they're getting a withdrawal bleed, when they stop the progesterone, then it's a time that, you know, it's like kind of like we're on the unknown. You're on the oral contraceptive.

01:03:18:09 - 01:03:24:00

Dr. Jaclyn Smeaton

You could like, take a placebo pill for an extra week, just not bleed on a vacation. You kind of know when it's coming.

01:03:24:01 - 01:03:25:00

Dr. Felice Gersh

Exactly.

01:03:25:00 - 01:03:25:21

Dr. Jaclyn Smeaton

You know, you plan.

01:03:25:21 - 01:03:28:00

Dr. Felice Gersh

Your life, you can plan your life.

01:03:28:02 - 01:03:52:05

Dr. Jaclyn Smeaton

Then what am I? And there's no right or wrong way. We're all this is we're in a learning phase of menopausal hormone therapy. Thankfully, we have some studies. What you're talking about the physiologic dosing is more is a higher dose than is typically put into like standard practice guidelines. I want to be clear about that. So if people want to learn more about, they should talk with you and take some of your classes, because it is a whole nother approach that you could consider.

01:03:52:05 - 01:04:21:04

Dr. Felice Gersh

It is important for people to know that the standard of care for women who have early onset of menopause, or what we call premature ovarian insufficiency or early early menopause so early is from 40 up to 45. And premature is before the age of 40. The standard of care not based on studies based on, quote, expert opinion. No studies is to give physiologic cyclic hormone therapy.

01:04:21:06 - 01:04:47:21

Dr. Felice Gersh

What I am recommending is basically what is the recommendation for women who go into menopause early. All I'm saying is, why would we not continue that? Because the standard recommendation is to stop it between 50 and 52, the sort of average age of menopause, and then go to the daily routine of a little progesterone and and estradiol every day.

01:04:48:02 - 01:05:16:20

Dr. Felice Gersh

Up to that point, they were recommending physiologic cyclic hormones as the standard of care. So what I'm saying is, which is not the standard of care, why are we stopping it? That's all. You know, why don't we just continue it? The only difference is that I don't recommend the oral progesterone, which I did for years. For years I recommended oral progesterone until I did a deep dive and I was like, what the heck, you know, what are we doing?

01:05:16:22 - 01:05:37:19

Dr. Felice Gersh

And there is published data. There's a ton of data in the infertility world. Of course, in terms of menopause, there are studies published, never enough, and we definitely need more. But it's not like we're in a complete void of any data. There is data, and we do know what kind of levels are achieved and what it does to the endometrium.

01:05:37:19 - 01:05:59:16

Dr. Felice Gersh

And I just wanted to throw in there's actually published data. I know it sounds weird until you get over it, but there's actually published data on rectal insertion of progesterone tablets, which give you extremely good absorption and really good systemic levels. And so we do have published data on that. We don't have a lot of clinical studies. Of course we don't.

01:05:59:18 - 01:06:22:06

Dr. Felice Gersh

But we have clinical data on just what it does that it does get absorbed really well. And so if somebody say wants to have sex and they want to use an alternative, there is published data that it does work. I mean, we don't have the clinical studies looking out into the future, but it's not like we're doing something that's never been done, never published.

01:06:22:08 - 01:06:22:23

Dr. Jaclyn Smeaton

01:06:23:01 - 01:07:00:07

Mark Newman

We went into, several different as these conversations go into several different, areas. And one of the things I think is conversationally hopping from continuous oral to cyclical vaginal. I was just wondering if you could state really clearly for, this slow minded guy, Doctor Gersh, when you stratify those in terms of like both of those moves, how would you weight those or grade those in terms of the the value of reconsidering continuous and the value of reconsidering using vaginal in terms so route of administration and then continuous versus cyclical.

01:07:00:13 - 01:07:09:23

Mark Newman

Which of those do you see as being maybe more important for like reconsideration for, for women if that makes sense.

01:07:10:01 - 01:07:23:13

Dr. Felice Gersh

I don't know that I can do that. I would say that if I had to pick, which is the bigger

deal, I would say cyclic is bigger than okay, but I have I don't, but I don't feel good with that at all. So I won't do it actually.

01:07:23:15 - 01:07:26:11

Dr. Jaclyn Smeaton

Because like you asked for, to pick a favorite child.

01:07:26:13 - 01:07:47:03

Mark Newman

I like the fact that it's difficult though is an answer. Right? And the other thing is, I think it seems to me we're very critical often of when medicine studies one variable in any particular thing, like you get off on the wrong, like down the wrong path. And I think that that is, an example of that, right?

01:07:47:03 - 01:08:05:22

Mark Newman

Where when you're studying the state of the endometrial only and that's the only thing you're thinking about, then you can build a case for continuous versus cyclical. And what I hear you saying, and again, my brain is not the clinical side. So I'm just trying to understand this as clearly as I can is when you start thinking about all these other factors.

01:08:06:00 - 01:08:44:03

Mark Newman

That's where, you know, a case can be built for, you know, exposure and not exposure, having having a cyclical approach to progesterone that does mimic more what the woman's been exposed to since they started, you know, cycling, in their teens or 20s or whatever. So that's, that's a helpful thing for me to just sort of be thinking about more and watching for more of this research and thankfully, we know that there's there's relative safety with what the majority is doing in terms of using bioidentical estrogen and, and probably giving it transdermal and then countering that with, with progesterone, either oral or progesterone.

01:08:44:03 - 01:09:00:16

Mark Newman

And, you know, we didn't even get into the topic of, of the what the safety data says with transdermal, and all of that. So it's, it's fun. How many endless different, different roads this conversation can go down. And I really appreciate your, your, your perspective and, and input on it. So.

01:09:00:18 - 01:09:23:21

Dr. Jaclyn Smeaton

Mark, just one thing that I'm hoping you can cover before we close is around monitoring of progesterone, because we take a pretty strong stance at dads on this, and I think it's an area of common confusion. So I'd like you to talk about that if you're open to that. Like when we're doing testing for postmenopausal females who are on menopausal hormone therapy, there's utility in understanding progesterone on a test.

01:09:23:21 - 01:09:28:06

Dr. Jaclyn Smeaton

But it's not always what people think. And when it comes to monitoring dosing, what about that for us.

01:09:28:06 - 01:09:50:04

Mark Newman

Yeah I mean it's another topic where like history has been very complicated. So Doctor Gersh said rightly that when you take oral progesterone, you don't get very big levels of progesterone in serum. But when you go back into the 80s, you used to because the testing was crappy. So you have these immunoassays that track really well with progesterone, but as soon as you use it orally, they become inaccurate.

01:09:50:07 - 01:10:11:20

Mark Newman

And so there's this, this interest. Well, for a lab guy, it's an interesting history. Probably not interesting for lots of details. But but what it comes down to is the with progesterone and the main message of progress from the main thing that that any of you doctors are trying to achieve with your patients, which is to make sure that the endometrial is protected, the lab testing isn't helpful.

01:10:11:20 - 01:10:33:19

Mark Newman

And I think that's where the lab industry can go wrong in, you know, kind of trying to jam square pegs into round holes and saying that, you know, the lab testing has utility and it really doesn't for asking that, question of like, did I get the dose right to protect the end of year? And we don't have answers, for that in the labs, we have answers, as you guys have rightly leaned into, into the studies of which doses work for protection.

01:10:33:19 - 01:11:05:19

Mark Newman

We know that in the labs just they I think they help with Astra dial. I think they help with testosterone in terms of like, did I get my dose right? But with progesterone, I don't think the testing is helpful for either oral or vaginal. Progesterone. The the two proven, routes of administration. We are admittedly a little bit in the weeds in saying, hey, there might be some extra value in looking at that metabolism profile to say how how your body's making that aloe pregnant on what your body's doing with the progesterone, I think is interesting.

01:11:05:21 - 01:11:30:10

Mark Newman

In some cases it's leverage able when we see very strong or not very strong analgesic effects from progesterone, the metabolites might offer some insight. But, but we oversell the lab testing as part of the MTX process when we try to ascribe too much value to monitoring progesterone, because the the primary job that it does just isn't spoken to.

01:11:30:12 - 01:11:55:06

Mark Newman

By the lab. So we, we really want people leaning into the labs where they're useful, getting your estrogen and your testosterone dose. Right. Absolutely. How your body's breaking down estrogen, breaking down testosterone. Am I making DHT? Am I making those metabolites we don't want absolutely useful? And then also interesting how the body's breaking down progesterone. But for getting the dose right, it's only, you know, a little bit helpful and in some cases, not at all.

01:11:55:08 - 01:12:14:00

Mark Newman

So, I think that's important to keep in mind, is to not overleveraged the labs where they aren't helpful. And I think progesterone is kind of one of those areas, where it has very good utility when you're not on HRT and then, mild and in some cases no utility when you start adding progesterone specifically on board.

01:12:14:00 - 01:12:14:13

Mark Newman

So.

01:12:14:15 - 01:12:33:02

Dr. Jaclyn Smeaton

Well, I'm really appreciative of both for making the time for their conversation. Say it's really important. And I can't wait to look back on this podcast in a couple of years. And we have more and more data, to draw a tighter conclusion over time. So let's keep researching. Let's keep getting some answers and see what we can do to help treat women better, which is what we're all here for.

01:12:33:04 - 01:12:37:15

Dr. Jaclyn Smeaton

Doctor Gersh, what is the best way for our listeners to, like, follow you or learn more about you?

01:12:37:19 - 01:13:04:02

Dr. Felice Gersh

Well, I have an Instagram, you know, like everybody and I do Instagram lives and I have a YouTube channel and I'd love for people to follow me. I try to post a lot of what I think is interesting and up to date kind of information. And I have three books, two on PCOS. Now. We won't get into the name change on this one, but, using the old name PCOS and one on menopause.

01:13:04:02 - 01:13:27:20

Dr. Felice Gersh

Menopause, 50 things You Need to know, which I think is like the perfect little handbook for every woman who is pre or post menopause anywhere in the in the journey. And I have a medical practice. I'm very old fashioned. I actually have a brick and mortar medical practice where I see patients every day in person. I also do telemedicine is called the Integrative Medical Group of Irvine.

01:13:27:23 - 01:13:42:19

Dr. Felice Gersh

I'm in Southern California and I see people I see patients all the time. I'm a clinician. I'm not just a talker, I'm a clinician. I see patients and and that's that's my primary job and my primary passion.

01:13:43:01 - 01:13:59:13

Dr. Jaclyn Smeaton

Well, we love that. And we love you. And thanks for joining us today. We'll make sure we put all the links to all the different places you can find Doctor Gersh and her books in the show notes. So be sure to check that out. And thank you to all of you who are

listening today. I hope you found this conversation as fantastic and in-depth.

01:13:59:13 - 01:14:18:18

Dr. Jaclyn Smeaton

Like, this is the kind of stuff we love to talk about and debates this is a great conversation. Take a deep breath. Catch a lot, catch some sunshine. Clear your head before you go see your next patient. But really, thank you so much for joining us today for this fabulous conversation. If you want to learn more about hormones, if you like this type of conversation, we do release a new podcast every Tuesday.

01:14:18:18 - 01:14:28:10

Dr. Jaclyn Smeaton

So also be sure to click subscribe so you can follow the podcast and you can follow us AG test on all the socials. We'll see you next week.

01:14:28:12 - 01:14:33:16

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