SARAH BERGA: Well, it's a little early to have this lecture in German, so I converted it to English for you today. Actually, this is a fun topic. It's a fun topic because it's really controversial. And everybody is always asking this question to me in the office, and that is, are hormones going to help me with my cognitive fog?

So I'm going to try to dance around that topic right now, because, one, it's hard to study. Two, everybody's got a different perspective, and what you consider to be evidence is going to be user dependent because we really can't do a randomized clinical trial on this one. So I'm going to give to you a perspective, I hope, for thinking about this topic so that you can help people understand it.

From my perspective as an OBGYN, I was delighted to read one time that children do better who have grandparents. And they have less illness. They do better in school. And I thought, you know, that's one of the reasons to do this well-- is that if we can save grandmother's brain, we actually help the next generation. So that's my obstetrical tilt to this. We have known for years, but not woven it into our clinical thinking, that hormones affect the brain. And I'm going to talk to you a little bit about how they affect the aging brain.

This is a patient that was in the newspaper in 2004. And she said she was taking hormones, but at the time of the WHI, she decided she should stop. And it was a self-imposed decision, and then she noticed she, quote, "wasn't as sharp as she used to be." How many of you have ever had a patient come in with something like that? And what did you tell them?

So which of the following are recognized indications for the use of hormone therapy after menopause? A, prevention of diabetes. Weight loss. Prevention of cardiovascular disease. Improve sleep architecture. Neuroprotection. And bone fracture prevention. So how's the audience response? OK, well you guys got it right. It was obviously too easy. It's bone fracture prevention. So do you think any of these other things are true, such as prevention of diabetes?

It turns out that prevention of diabetes looks to be the most important finding from the WHI. That actually, use of hormones markedly reduces the risk of diabetes, but it's not a recognized indication. Neuroprotection is one of the areas where there's a 50/50 split. Some people saying that the hormones cause dementia, and some people saying they actually prevent against it. So we're going to go through that one because it's the most controversial.

So there are indications for hormone use, and they typically fall into these categories, symptom relief, disease prevention, disease treatment, anti aging, and health promotion. So you have to think about it from each of those perspectives when you've got someone in the office with you, including someone that's complaining-- what I like to call cognitive fog.

So the perceived risk/benefit ratio is going to depend on what the person thinks they're there for. So if they're there to feel better, feel sharper, then you've got one set of indications. If they're there because they've got a known risk of diabetes in the family, and they have read the WHI, and they're smart-- like somebody that might be an academic in our institution would walk in and say that to me-- then you've got a whole different conversation going. And different professional societies give different guidance. It's very, very confusing.

So being a reproductive endocrinologist, I had to pick, American College of OBGYN, or my favorite organization, The Endocrine Society. So I've been with The Endocrine Society as a member since 1986. And I really think they're wise. Rick Stanton actually did this with a committee, and published it in 2010. And The Endocrine Society uniquely has developed this system called GRADE, so that they don't have to throw out all the data. So they actually coalesce data from lots of different perspectives, and then they rank the data and grade it A through D, or E, actually. The actual grading system was published in 2008.

So the Women's Health Initiative-- and I served as a co-investigator for the entire time I was in Pittsburgh-- was a wonderful study, but it had some limitations, one of which was drop in and drop outs. And that, actually, for a randomized clinical trial can be fatal, because you have to do what's called an intention to treat analysis. But if there's no one left in the categories under intention to treat, it's going to be hard to analyze the data. So they had to do a lot of backward flips to get the data to reveal to them what they thought was going on. And at the end of it, they've published retraction after retraction after traction. So when they came to 2009 to actually weigh the evidence, they threw a lot of it out.

So here's what The Endocrine Society thinks is the evidence. Grade A evidence for estrogen or estrogen plus progestin after menopause. So you can read it rapidly here, and you have it in your slides. So the bottom line from The Endocrine Society is, if you want to improve cognition, you have to start hormones before age 60. Here are all the other things that they think are going on as well. And we can talk about this later. Here's the grade B evidence. And I just actually took a 66-page document and condensed it into four slides, so pardon the brevity.

But as best as they could determine, based on data in 2009 and then published in 2010, the overall reduction in mortality for use of hormones after menopause, was roughly 40%. That's kind of dramatic, and probably different than what you've been told. And again, I do know that this is controversial. So we can actually do this later, maybe even offline. I don't want to steal anybody's time. But I want to show you the next one on the list, reduction in diabetes. And we'll talk about that in a minute.

So think about the brain. Think about insulin. Think about diabetes in the brain. And you'll realize that some of the effects of hormones are actually through the improvement of metabolism. And I'm going to actually hit on that topic a little bit harder. So if you took women 50 to 59 and less than 10 years after menopause, and looked at events per 1,000 women for five years of use of hormones, here's the best estimate based on The Endocrine Society. So it would be a protection from breast cancer and heart disease. Now I know if you haven't read this, it's probably going to be surprising, because this is just the opposite as what is in common knowledge. You would see a reduction in fractures and overall mortality. And a very marked reduction in the risk of diabetes.

If you combined it with progestin, you would see less benefit for cardiovascular. And that's something we've been saying for years. A protection from endometrial cancer, a reduction in fracture, a reduction in colorectal cancer, reduction in mortality, and still a reduction in diabetes. If you take oral estrogen, actually some of these risks go up. And we can't go through all of that today. But oral estrogen is thrombogenic. And we think that part of the reason the benefit isn't as good with oral estrogen, is that it is thrombogenic. And so then you see that there's an increased risk of VTE and stroke with oral estrogen, and that that is the same whether it's combined with progestin or not.

So issues deemed most critical for the future were, what products are best? What are the optimal routes and products? And what are the optimal doses? So we've done none of that, so far. We need to, also, be able to identify the women most at risk and those most likely to benefit, so that we can develop new approaches. So the pharma industry hasn't given up on this topic, but there was this certain hiatus in investigation after the WHI because people were nervous.

So back to the topic of the day. Do you think that postmenopausal hormone use will foster better brain health? And mental fog is an interesting complaint. It's in my office almost 100%, because people who are feeling well don't run into the office. And I'm not in the health prevention world, so I'm seeing people who are actually having trouble. And one of the main findings is word finding. So they have trouble deciding what they're going to say. They feel irritable and they have reduced libido. All of this is really distressing if your brain used to work well, and all of a sudden, it's not working as well. People, after their reproductive years, are going to complain that this is not what they were anticipating.

There's also a marked increase risk in neurodegenerative disorders if we do a premature surgical menopause. So if you take out ovaries before age 50, there are studies that convincingly show an increased risk of neurodegeneration. So that begs the issue as to whether or not actually hormones are neuroprotective. And that's actually when this topic got revived. So surgical menopause actually teaches us that the brain is really subject to hormones, and that it is a positive modulator of brain function.

So which of the following is a recognized consequence of perimenopause? Bone fracture, diabetes mellitus, depression, hypertension, or weight loss? You got that one right too. Too easy. Actually depression has been-- well bone fracture too-- but depression is a consequence as well. I got the wrong answer there. Maybe I marked it wrong on the thing. It is depression.

So this is the study of the SWAN, the study of women across the nation at midlife. And it showed what other studies had showed in the past as well, which is that there is an increased risk in depression during the menopausal transition, which we refer to as the perimenopause. And this increased risk of depression sort of begs the issue of the brain as a target tissue for sex steroids. And it asked the question implicitly as to whether or not hormones will help with this mild depression that seems to accompany perimenopause.

So soundbites for busy practitioners are that not all women are the same. And I never had anyone fight me on this one. Not all estrogens are the same. And I've had lots of people fight me on this one, including Jacques Rossouw, who was the head of the WHI. Not all progestins are the same. Most people don't have an opinion about that one. But to be able to foster better brain health, we have to understand all of those aspects.

So what matters? And what matters most? So it's hard to save a failing brain. If someone has already signs and symptoms of neurodegeneration, it is true that hormones may make it worse. And there are meta-analyses that show if you give certain hormones you can really markedly accelerate neurodegeneration. The estrogen type has been widely debated. There aren't very many head-to-head comparisons, and so there's a lack of information. But most people believe that the cognate ligand, which is estradiol, is likely to be best.

The route of administration has been debated for years, but I would say the preponderance of evidence, at this point, speaks in favor of non-oral routes of administration. The timing of initiation is where we really are focusing most of our attention right now. And the bottom line is that any hiatus is bad. So if people actually try to tough it out, and go 10 years, and then come back to you for hormones, that's probably non-optimal. And the duration of exposure, that's the hardest one. I don't really think anybody has a very good clue as to how long women should actually take hormones.

But what are we up against? This is the hypothesis, that by giving hormones early in the right dose we're going to actually slow aging. Now that's a pretty big idea. And to be able to do this well, we really have to know what we're doing. And because we haven't invested in this question very much, more opinion is available than is evidence. And the brain is kind of a complicated organ. So what's a gynecologists doing talking to you about the brain? I'm talking to you about the brain because it's the most important reproductive organ we have. And it's very complicated.

So different parts of the brain respond differentially to hormones. And for years we really didn't pay much attention to the non-reproductive effects of hormones on brain. But I've listed some of them here. And these are the ones that actually drive and underpin the complaint of not feeling as sharp as once did. And the incredible complexity of the brain, actually, is also leading to an incredible complexity of hormone action by multiple different mechanisms I've listed here. So you don't have to know all of this to appreciate that the brain is really complicated. There's lots of different neurotransmitter systems. And we've been trying to amass information about this for the last 30 years using modern technology.

One of the things that we have discovered-- and I know that this is not surprising-- is that the brain of men and women is markedly different. It's possibly the most dimorphic part of the body. So I just say that to wake you up. So the differential parts of the brain from men and women are shown here. So the areas in red are larger in women and have a different organization than the areas in blue that are larger in men. And so what we've learned from that, is hormones actually impart their actions differently in men and women. So estrogen would have one set of effects in men, and a different set of effects in women. And that actually is a relatively new concept that people are working on.

Now imagine my dilemma, I have to explain all of this to you, and you're a mixed audience. And so one half of your brain is listening to me with whatever you're doing, and the other half of your brain is listening to me with a different kind of input. So some of you are listening to my tone of voice, and some of you are listening to the content. And not everyone's on the same page. And this tends to break out by sex.

So if you look at storytelling, and you ask people what they heard-- and that's what they did in the study-- and then asked them to repeat what they learned, men tend to remember the details of the story, and they tend to use a different part of the brain to listen to the story. Women tend to remember none of the details, but get the main picture, and can't remember why they came to that conclusion. And they are using the same part of the brain, but the opposite side.

So we call one of those centers the detail center, and it's the amygdala, and in men, it's online for details. And for women, they're listening to the details, but that's not the main picture. And they're listening to the big picture side. And so imagine after the story is told, they tell each other the story. Well, they won't have heard the same thing. So in telling you this story today, I have to have some details for people who like that, and some big picture stuff for people that like that. And I know I can't get it perfectly right, so I ask your forgiveness in advance, and to remember that hormones are actually the reason we have this difference.

So the brain is complicated. It's got lots of moving pieces. It's got lots of neurotransmitters. And it's also an energy hog. So it's 2% by weight, and it takes up 25% of our daily calorie intake. Takes about 16% of our cardiatic input. So it's just a huge energy hog, and it likes to be fed.

One of the hormones that keeps the brain alive is thyroid hormone. And if you take away thyroid hormone, what do people say to you? They're cranky. They're not happy. They're slow. They feel depressed. Life isn't good. And then if you give them back thyroid, they feel better. And when we look at the parts of the brain that are impacted by low thyroid, there aren't that many. So imagine these tiny little bits of the brain being offline suddenly lead to pretty profound behavioral complaints. And that's the same with hormones.

So I'm going to show you some pretty pictures. So how would we figure out if hormones are neuroprotective? It's a pretty big challenge, lots of pieces to this puzzle. So limitations of our current understanding of the pros and cons of hormone use include which of the following? Smokers weren't included. Lack of inclusion of older women. Oophorectomized women not included. Few longitudinal head-to-head comparisons. And no studies comparing estrogen treatment with an estrogen plus progestin arm, so estrogen alone plus estrogen plus progestin. So few longitudinal head-to-head comparisons. And that's the problem.

So the question before us today is, do sex steroids promote plasticity, maintain brain function, and confer neuroprotection? And this is like balancing a teeter totter, because we know that estrogens are actually growth promoting. And if we give too much of something that's growth promoting to an older cell, it tends to make mistakes because it's growing too fast and it's cellular machinery is old. And so we have to balance it by stage, or age, of the cell.

And we also know that one of the expensive parts of the brain are synapses. They're very hard to maintain. They take a huge amount of energy. They might be what that's all about when we think about the energy dependence of the brain. And by the time you miss about 25% of your synapses, you start to have mild cognitive impairment.

You can't really see synapses on neuroimaging quite yet. We're getting there. But we know that synapses are what it's really all about, because each neuron in your brain has about 10,000 connections. So it's a pretty good supercomputer. And we want to maintain those connections.

So we sometimes have to use animal models to look at this. And we'd like to use an animal model that's close to us. So this is the animal model called monkey. And they had oophorectomy performed to young and old monkeys, and then looked at the synapses, which we call dendritic spine density. And we looked at it in prefrontal cortex thinking brain and visual cortex.

And brain A is synapses off hormones for three months after oophorectomy. And then brain B is that same brain with hormones added back in. And the black dots are synapses. So which brain do you want, brain A or brain B? How many want brain A? How many want brain B? Right, more synapses make for a faster brain. And we think that those synapses are maintained by estradiol in women.

So to get our arms around this, people have been doing neuroimaging tasks. They've been giving people reading task, or visuals task, motor task, and looking at what happens on and off hormones, and then looking at the people in the neuroimaging machine. So this is the first study to look at reading ability and hormones. It was done by Sally Shaywitz. And she showed that, actually, just a single month of hormone exposure led to an increased ability to read in older women who are postmenopausal, and that that correlated with the change in the part of the brain that handles phonologic tasks.

This is another study that just came out a couple of years ago. This is the only one I know that really looked convincingly at conjugated equine estrogens, otherwise known as Premarin, versus 17beta-estradiol, which comes in many different forms, many different preparations. And what you will see here is that for certain tasks, like attention, estradiol appeared to be a lot better. For verbal memory, estradiol appeared to be a lot better. For visual memory, it wasn't different. And so the bottom line from most people right now, is that verbal memory is the most sensitive to estradiol, or estrogen. And so people have been trying to look at that part of the brain.

And this is a study looking at estrogen therapy and prefrontal cognitive processing. And you can see these are the parts of the brain that are maintained on estradiol in this study. So this is 12 weeks of transdermal estradiol given to postmenopausal women, and marked enhancement of activity when given a phonologic task.

And these are further studies, different study, but also looking at parts of the brain that are now maintained during task when on hormones. And this is looking at a brain that's depressed. So the not depressed brain lights up brighter in the neuroimaging machine. And this is a serotonergic binding activity. So the theory of depression is that it's not enough serotonin around, and lo and behold, the depressed brain doesn't show much serotonergic binding in key brain areas and as compared to a not depressed person.

So this is our study. We gave transdermal estradiol for 12 weeks to recently postmenopausal women who were not taking hormones for at least 12 weeks, and looked at serotonergic binding in key brain areas. And what you'll see is the brain areas diagrammed off to the side with a MRI. And there are two brain areas that we looked at. One is called dorsolateral prefrontal cortex. And the other is anterior cingulate cortex.

And anterior cingulate cortex is your social intelligence center. I sometimes call it the cocktail center, and it lets you know what people are thinking. We actually think it's very important for parenting, and for teaching, and for all the things that allow us to surmise what's going on with people. The dorsolateral prefrontal cortex is your addition, math center, your verbal finding center. And it tells you when you've made mistakes. So both of those brain centers light up when women are given hormones for 12 weeks. So we think there's more of the brain to engage in those tasks when on hormones.

Same thing in monkeys. This is looking at a different kind of neurotransmitter. Every neurotransmitter that we've looked at is increased in its activity in key brain areas when given estradiol. This is my favorite. It's a old study that has been reanalyzed. And it started when the WHI came out. And they asked women to either discontinue hormones or not. They were randomized, and then they looked at brain metabolism. So we talked about the brain being very energetically dependent. And what was found in this study is that women who were on hormones for two years longer actually had far more brain activity than women who were off for two years.

So this is the recent update of the same study. It first was published in 2010. And then they just updated it in 2014. And I'm not going to go through all the details, but I commend it to you. If you'd like to read it, it's a pretty interesting study. And so instead of randomizing women on to hormones, they actually randomized women off hormones, and then looked at those who had taken the hormones for longer.

And I really do think they convincingly showed that the brain is much happier on hormones. And this is some of the data for this. Now remember the thyroid analogy. It doesn't take much of the brain to be offline for people to complain. Conversely, it doesn't take much more for the brain to be happy. So a little bit of increased metabolism in key brain centers actually leads to a better feeling brain.

So I'm going to skip over all this. This was a meta-analysis that was published. And basically, the bottom line of this meta-analysis was to look at progestins. And the most impairing progestin-- and all progestins impair metabolism, but the one that impaired it most was the one that was used in the WHI, which was Provera. So madroxyprogesterone acetate was by far the worst progestin in this meta-analysis.

Now, if you like monkey studies, I'll show you this one. This is my favorite one. So people have to get along, and monkeys have to get along. And female monkeys given Provera, over here in this category, got along the least well. They've had more antagonistic behaviors than monkeys given just estradiol, or even estradiol plus micronized progesterone. So if you want to make people cranky, I recommend Provera. So imagine WHI was a study of a weak estrogen, conjugated equine estrogen, and a pretty toxic progestin called madroxyprogesterone acetate. And it's remarkable to me that people didn't feel any worse than they did in the study.

So we also know that feeling bad actually has cognitive side effects. And so it's not funny if we actually make people feel bad. So if in fact the progestin that was used in the WHI made people depressed and cranky, that actually is going to impair, in the long run, their cognition as well. So that's kind of where we rest with this.

We also know that cortisol can interfere. And I don't have time to go through all of it, but basically, glucocorticoids have very different effects in men and women. And this is the study that was recently done here in North Carolina, at NIEHS. And the bottom line is that glucocorticoids suppress inflammation in male rats, and upregulate inflammation in females. And we think inflammation is one of the pathways that leads to neurodegeneration. So stress actually has the effect of increasing cortisol. And we think in females, it may actually be proinflammatory, and not be your friend. So stress may not be so bad for the male brain. May be much worse for the female brain. So that's where we are. We have to figure out how to do this right.

Can you imagine giving insulin in a one-size-fits-all? What if I gave you one standard dose of insulin? Half your patients would be OK, and half would probably not. What about thyroid? Anybody want to have a monophasic thyroid pill, not be able to adjust it? See anybody who's been on too much thyroid before? That's kind of dramatic, isn't it? [INAUDIBLE] all wired around. But someone on too little is bad too.

So we actually haven't figured out how to do this right. And all we've decided is that hormones are really important. But now we have to figure out how to do it for us. And these are pictures of why it matters. Our hypothesis right now is that we need something that approximates physiology, or less. So physiology is estradiol level of 100 or less, given transdermally or non-orally. And the reason to give it transdermally, as I said before, is the marked reduced risk of clotting when given non-orally.

And this is the first study to look at this. It came out at the same time as the WHI, and then it got ignored because people were paying attention to the WHI. So to get some more attention, they republished. And this time they looked at it in a much larger circumstance, so 27,000 women. That's enough. And this showed that if you took transdermal estradiol, you actually had almost a reduced risk of VTE.

So think about that in the brain. So stroke is essentially a thrombogenic event in the brain. And low doses of transdermal estradiol actually don't increase the risk of stroke. But high doses of any estrogen will because you tend to tilt toward thrombogenesis. Different progestins are different in their thrombogenic ability as well. And the most thrombogenic progestin is madroxyprogesterone acetate, the one in the WHI.

So we think the transdermal estradiol works by, actually, in part preventing clotting, but also by improving endothelial elasticity. We also think it works by reducing anxiety, which I don't have time to go through. But we did studies on women given different kinds of estrogens for breast cancer treatment, so these are SERMs. And then we studied women who were taking aromatase inhibitors, which get rid of estrogen altogether. Bottom line is that an Anastrozole, or any of the aromatase inhibitors impair the brain more than SERMs.

So does this help us put into perspective what's going on? Hopefully. So the sex differences is real. We've talked a little bit about that. The brain of men falls apart slower than the brain of women as we age. And that's what's shown on this side right here. So in slide A you see the study that's being done still. It's Cache County, which is in Utah. Prospective study of healthy men and women at age 65. And you can see that the men have a much lower rate of dementia as they age. And the women, a much higher rate of dementia as they age.

But women who took hormones after menopause for up to 10 years, actually have rates of dementia that approximate those of men. So think quickly about all those neural mechanisms that I've just reviewed with you including synapses, and think about dementia as a disease in which synapses fall apart. Then it actually is easy to understand why estrogens might be helpful for aging brain.

And we do know that men have estradiol. So I think sometimes men feel bad when I'm giving this talk. They think, where's my estradiol? Well you've got estradiol. And these are CSF levels of estradiol. So men have estradiol because testosterone gets aromatized in the brain to estradiol. Women have one source of estradiol, and that's the pre-menopausal ovary. And after menopause, that main source goes away. So women are hypoestragenic at midlife, and men are not. And we think that this explains the Cache County study, which has also been reanalyzed.

Now just for fun, how many of you know what is microchimerism? So microchimerism is the hot new topic. And this is another strategy for preventing dementia, but you have to take it when you're at reproductive age. So one way to get new neurons, is to have a baby because the cells of the baby go across the placenta and embed in the mother. And those cells are younger, and they live in the brain forever. They live in other tissues forever as well. And how do we know this?

So this is a study of XY bearing cells in brain of women who had sons. And we can do this in females, but we can't separate mom from baby, so they just used women who had sons. And what you see is these cells are basically repair mechanism for the brain. And so women who've had children, actually have extra cells that were given to them during pregnancy that help them with rates of dementia. I thought you would just want to know something fun and titillating. I find that interesting.

So back to the main topic. Using estrogen helps cells stay alive, and it probably even helps those fetal cells stay alive. This is the Olmsted County study. This is the one that looked at prophylactic oophorectomy before age 45 and found that doing so increased the risk of death, increased the risk of depression, increased the risk of Parkinson's, and increased the risk of dementia. And this is the question in reverse, right? This is not giving hormones, this is taking hormones And if you take hormones from women too soon, they fall apart.

And that was also found in the Nurses' Health Study. There was no age group in which doing a BSO was associated with improved survival. For years we have taught people to do a THBSO as a kind of cure all for everything that ails you at midlife. And in no circumstance is this helping. And this is part of the evidence behind the recommendation to use hormones. So as I told you, the WHI had to go back and reanalyze all their data. And what they found is that any woman who had used hormones prior to enrolling in the WHI had a reduced risk of all-cause dementia.

So I hope I have convinced you that hormones impact the brain. I'm sorry that we don't have a really definitive RCT. I don't think we ever will. I think we're going to always have to put the pieces of the puzzle together. I think we don't have enough data to say what the right dose exactly is. But I do think we do have enough data to say to use transdermal estradiol, and to be careful about the progestin that you use. And that's the hardest part of the story right now. Use of SERMs is probably better than aromatase inhibitors, particularly for women that have to use something because they've had breast cancer.

We see the same phenomena in men. And I haven't had time to talk about that, although that's one of my favorite areas is to compare and contrast. So men who actually have to have a orchiectomy, or have to have GnRH agonist, actually see an acceleration of cardiovascular disease in much the same way that women who have a oophorectomy have an increased risk of cardiovascular disease. So we think the non-oral route is better because it minimizes VTE risk, it gives greater vasodilation that lowers blood pressure. And it's neutral for stroke risk. And that cannot be said for oral estrogens.

There's a lot of information-free zones. So I will gladly recognize that this is just the best guess. But if someone comes into your office, you owe them the best guess you can get. This is the best guess I can get. So hormones aren't going to benefit everybody, but the healthier someone is actually-- it's not a healthy user bias effect. It's a healthy user effect. If you are healthy, it's going to be easier to keep your brain healthy. And so it's important to remember that as we go forward.

So what should we tell Jean Mortimer about not feeling as sharp as she once did? Should she discontinue hormones, and try to stay off of them? Or should she stay on them? OK, thank you very much. I really appreciate it. So this work has been funded by you for many years, you're taxpayers. NIH has funded a lot of it, and actually some pharma companies have funded some of it as well. It's been my privilege to be working with a huge number of really intelligent people that have made me look smarter than I really am. And I am here all day long to talk to you. Thank you so much.