Emily: I'm Emily Kumler and this is Empowered Health. This week on Empowered Health we're going to look at the treatment options for perimenopause[1] and sort of menopausal changes and we're going to consider some of the controversy that surrounds hormone replacement therapy[2] and what that means for different women. We're going to start by talking to a doctor and researcher from Mass General Hospital here in Boston.

Dr. Shifren: My name is Dr. Jan Shifren [3]and I am the Vincent Trustees Professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School. I'm also the director of the Massachusetts General Hospital Midlife Women's Health Center.[4]

Emily: So I think a lot of people are familiar with menopause being the phenomenon where women don't get their period for the 12 months prior. But what is perimenopause? How do you define that?

Dr. Shifren: Menopause[5] is better known to women. Menopause is the time of life at which the periods have stopped and the ovaries are no longer making estrogen. It's important for women to realize that menopause now for the women in the developed world is about a third of their lives. So it is really important that women make this phase of life, you know, healthy and productive and just as you know, as healthy as they can. Perimenopause is a more complicated definitions. So perimenopause is essentially the leading up to menopause. So we used to think that it was a, it represented, you know, a gradual decline in estrogen[6] levels until you get to menopause, when the ovaries no longer make estrogen. But what we've realized through research is actually it's more of a time of ovarian chaos.[7] So there are some months when the ovaries are actually making a lot of estrogen, even more than they might make in a typical menstrual cycle. And then all of a sudden there's a month or

---

[1] https://www.mayoclinic.org/diseases-conditions/perimenopause/symptoms-causes/syc-20354666
[2] https://www.mayoclinic.org/diseases-conditions/menopause/in-depth/hormone-therapy/art-20046372
[3] https://www.massgeneral.org/doctors/doctor.aspx?id=16440
[4] https://www.massgeneral.org/obgyn/services/treatmentprograms.aspx?id=1798
[5] https://www.mayoclinic.org/diseases-conditions/menopause/symptoms-causes/syc-20353397
[6] https://www.hormone.org/your-health-and-hormones/glands-and-hormones-a-to-z/hormones/estrogen
[7] https://watermark.silverchair.com/jcem1495.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAkYwggJCBgkqhkiG9w0BBwagggIzMIICLwIBADCCAigGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMUbVLXkSRIW8qXbuNAgEQgIIB-WUZrEpCOh-y34eIs3SNBumBjwDdM4fQ-bFHPmCG7PICJNlZDlyfTICdpCC5L94HU0dSK_TWj1PswsGOoyNnR6Ct4jqegeh9Z7J2irlEbXaO46qKVYRfHBmM0-AyFfq20J-AhBCtpUdZobzhrrzjpSzhKBnqRbgIC9thW4j84IrEMdffjP0dLjO_zCCz6R4OQ7fjdzjLN-nK_oip441ZIvUSDyP-kUuMfPtsT7Vvf2meuFtQJyVsPpJ9HpFHVtEQnslJmUVhsjoPb1lERVwkdHAeKsLlcKsU9qOmXzemLQv6W0Si-vQKECmmq3mwMte5MOsIGimayOlSkYJPG-KwVsPbTjChdK5o3udvQp5t1_FkmFf2zpxYqGBg_LOwqY5me_XE4OZJjckVTQ_gKKxREPfVLhxj3AwlvRyFrAeggdvgpxxwYFDoOb9R1190cBmTd3yyBOtuFYXdblj6w6bLQ0_Vk68UMAWuTUNcyBTgMPJeyeAHQXEVUSTZp-l5lRrEcdWdGcjsi4Qox_qa6G7BgyoRGgL9rNHhOsHJnXg7Tl8GQDe1rf2tEVi6KwlWgFYHZNXqFYaTatIf9AKv6pawGM5A_VIapV9bk0CxzU2dZaev4cOALzykkJluyWvll7cx17fSEa_oCllGNBMd9fztvcftFP7aY_ZCaik

two or three where the ovaries aren't making anything and then they perk back up again. And you may have another month or two or three or six where the ovaries are cycling again. The perimenopause or another way to describe it is the menopause transition. I think it's actually much more difficult for women than menopause itself. And that's really because it's so unpredictable at the times when the ovary is not making estrogen, a woman may experience typical estrogen deficiency symptoms such as hot flashes, night sweats,[8] sleep disruption[9]. And of course when you're not sleeping well, you then have day times fatigue, you may be more irritable, you may have difficulty remembering where you left your keys. And a lot of that is just sleep disruption and this, you know, poor quality of life because of all the symptoms. And then all of a sudden the symptoms go away and you're feeling fine for several months and then they come back. So it's a really challenging time for women.

Emily: Well, and I think especially because we're all so used to sort of being programmed around when we get our period and like the sort of even, you know, knowing when you opulate and that sort of cycle being irregularity, that sort of a pattern that you've had since you were an adolescent. And then to have this sort of irregularity introduced. I liked that it's called chaos– that it's like chaos. Right? But I also think what's really interesting for me, and I don't understand this, so I feel like it would be great to have you explained it a little bit further, is when your body is not, or when your ovaries are going through, let's say a couple of months where they're not producing estrogen and you're having those symptoms, is it almost like a withdrawal? Like when people come through on the other side of menopause, they often say that they feel really stable and great.

Dr. Shifren: So absolutely. So, during the transition, we think that a lot of the menopausal symptoms, predominantly hot flashes and night sweats, are not just a response to low estrogen. Because as you said, you know, every woman over 55 typically is going to have low estrogen levels for the rest of her life unless she takes estrogen therapy. So it's not just a response to low estrogen, it is a response to estrogen withdrawal. And so that's what all the fluctuating ovarian function where some months the ovaries are making estrogen and some months they are not often is associated with really bothersome symptoms. I should mention that in addition to the hot flashes and night sweats and all the resulting symptoms of not sleeping well, there can also be vaginal dryness and discomfort with sexual activity[10] and so it is really important that women do speak with their healthcare providers about those symptoms. Well, we've discovered from research we've done is that unless a clinician asks,

[8] https://womenlivingbetter.org/night-sweats-hot-flashes/
[9] https://womenlivingbetter.org/disrupted-sleep/
[10] https://womenlivingbetter.org/vaginal-dryness/

women often are hesitant to discuss their sexual symptoms[11], particularly dryness, discomfort, and there are a lot of very effective treatments. So women really should be empowered to speak with their healthcare providers about those symptoms in addition to hot flashes, night sweats, and sleep disruption. I am shocked at how many women do not tell us that they're having vaginal dryness and painful sex and it's so easy to treat. And so how do you treat that? There are many effective treatments for menopausal or perimenopausal vaginal dryness and discomfort with sex. We often encourage women to begin with just over the counter products. There are a lot of lubricants which reduce friction with penetrative sexual activity. So those are great to use with sexual activity and they are non-hormonal, completely safe. You get them without a prescription at your local drug store. Then there are also something called moisturizers or vaginal moisturizers[12], and they again are nonhormonal purchased over the counter without a prescription, but those are really designed to retain moisture in the vagina. So whereas the lubricants are typically used before activity, the moisturizer should be used on a regular basis, like two or three times a week, often at bed time. In the same way that you moisturize your hands or face, you can really moisturize your vagina. At the point that the over the counter products are no longer really treating the symptoms, really the mainstay of treatment at this point in time are low-dose vaginal estrogen[13], those do require a visit to your healthcare provider and a prescription, but they're incredibly safe. So unlike hormone therapy or estrogen that we use to treat hot flashes, which has to raise your blood level of estrogen to treat the hot flashes[14], very low doses of estrogen placed directly in the vagina effectively treat the vaginal symptoms of estrogen deficiency, but don't raise blood levels. So I really reassure women that although the package insert will be the same as for the high levels to treat hot flashes, the FDA's required that unfortunately, I really try to reassure women that when they use low doses of estrogen directly in the vagina, FDA approved to treat dryness and discomfort with sex, they do not have to worry about breast cancer or heart disease or leg or lung clots.

Emily: And can you talk a little bit about that? Because I feel like that is a big point of confusion for the general public, right? Like there was this period of time where people were told like hormone replacement is very bad, and then that has sort of flipped back. Right.

---

11 https://journals.lww.com/menopausejournal/Citation/2018/10000/Factors_associated_with_developing_vaginal_dryness.7.aspx

12 https://www.mayoclinic.org/vaginal-dryness-after-menopause/expert-answers/faq-20115086

13 https://www.mayoclinic.org/vaginal-dryness-after-menopause/expert-answers/faq-20115086

14 http://www.bloodpressureuk.org/BloodPressureandyou/Yourbody/Menopause

Dr. Shifren: You know, and I hate to say it, that is really a whole nother podcast because to talk about systemic hormone therapy for hot flashes is another great topic, but that will get us away from perimenopause.

Emily: That's probably one of the key things that we were hoping to talk about with you.

Dr. Shifren: If a woman is having really bothersome hot flashes and night sweats at the menopause transition, hormone therapy is truly the most effective treatment. If a woman is still cycling intermittently, then she may actually just use birth control pills. So for a healthy woman in her late forties early fifties and non-smoker with normal blood pressure, birth control pills are actually very safe at the menopause transition. And the nice thing about using them for perimenopausal symptoms is they not only treat the hot flashes and night sweats by providing estrogen, but they control the irregular bleeding, which is another real problem with the menopause transition. So when women are sometimes cycling and sometimes not cycling, they can have these episodes of really heavy bleeding where they're actually soaking through their clothes and it's pretty miserable. And so one nice thing about using birth control pills to manage the menopausal transition symptoms is they also control bleeding. But for a woman with really bothersome hot flashes and night sweats, let's say a postmenopausal woman who now does not have to deal with any irregular bleeding because her periods have completely stopped hormone therapy remains the most effective treatment for bothersome vasomotor[15] symptoms. That's the term that we use to describe the hot flashes and night sweats. When a woman is menopausal as compared to perimenopausal. The good news is she can use really low doses of hormone therapy that treat the hot flashes and night sweats, but are the same blood levels as she would have had when she was cycling regularly. So in the perimenopause, we often recommend birth control pills because they suppress natural cycles and give back some hormones, but once a woman is post-menopausal and no longer cycling on her own, she doesn't need the really high doses of hormones provided by birth control pills. She can do really well just using just lower doses hormones, basically the same blood levels that she would have when she was cycle.

Emily: That's mostly estrogen that you're giving or is it progestogen[16] too?

Dr. Shifren: When we give hormone therapy for postmenopausal women with a uterus, she takes the estrogen to treat all symptoms, but then she also needs to use a progestogen to protect the uterus from the estrogen. If a

[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3185243/
[16] https://www.nhs.uk/conditions/contraception/the-pill-progestogen-only/

postmenopausal woman doesn't have a uterus, then she would take just estrogen alone.

Emily: And what are the effects in terms of the sort of bones, brains, heart, all of these other things that are negatively impacted by the decrease in estrogen when you're taking the pill or like does that help compensate for those difficulties?

Dr. Shifren: So a postmenopausal woman is estrogen-deficient and when she goes on hormone therapy, the principle indication for postmenopausal hormone therapy is the treatment of bothersome flashes and night sweats. If she's taking it for hot flashes and night sweats, the good news is she will also have some bone benefit and women do lose bone with the estrogen deficiency of menopause and they do increase their fracture risk. And when you go on hormone therapy for hot flashes, the good news is it's also preserving your bone density[17]. Because there are so many other safe and effective treatments for bone loss and fracture prevention besides estrogen, we typically do not use hormone therapy specifically for a fracture prevention indication. We use it for hot flashes, but women should know that it's also really good for their bones while they're taking it for their hot flashes. In addition, hormone therapy is really effective for treating vaginal dryness and painful sexual activity. Again, if that was a woman's least symptom, we would typically recommend really low doses of estrogen placed directly in the vagina. Those don't raise blood levels. And so that would be a safer option if the only symptoms were bothersome vaginal dryness. But for a woman who's having hot flashes and night sweats, she can take systemic hormone therapy, raise her blood levels back to where they were when she was cycling naturally, treat her hot flashes and night sweats and at the same time typically treat the vaginal symptoms and prevent bone loss.

Emily: And how has this advice changed in the last 10 years?

Dr. Shifren: In 2002, a very large study was published called the Women's Health Initiative.[18] And that the goal of that study was to see whether hormone therapy could reduce the risks of aging in older women. So it was really designed to say, hey, if we give hormone therapy to women in their sixties could we actually keep them healthier? And the reason for that is that before WHI there were observational studies that showed that women who take hormone therapy had half the risk of heart disease and of course heart disease is the number one cause of death in older women. And so anything that reduces heart disease is really important. You know, what we now know is that

[17] https://www.iofbonehealth.org/hormone-replacement-therapy-hrt

[18] https://www.whi.org/SitePages/WHI%20Hormone%20Trial%20Findings%20Questions%20and%20Answers.aspx

healthier women took hormones and a lot of that health probably accounted for the benefit we saw. Those were what we call observational studies, but those data were so consistent that physicians were actually starting to use hormones to reduce heart disease risks, even though it was not proven in a randomized controlled trial. So Women's Health Initiative was a very large randomized controlled trial, meaning they took women or post-menopausal and they randomized them to either hormone therapy or a placebo, essentially a sugar pill. Women without a uterus received estrogen alone. Women with a uterus received an estrogen and a progestogen. It's important to realize that WHI was done with one form of hormone therapy, what we would now consider a relatively high dose of an oral conjugated estrogen.[19]

Emily: It was an equine estrogen right?

Dr. Shifren: Yeah, combined with medroxyprogesterone[20] acetate. It may be that other formulations in doses have lower risks, but unfortunately, we will never have a randomized controlled trial of that length and duration and size to answer that question. So when I'm telling women about the risks and benefits of hormones, even though they may elect a different formulation, I still share the risks that we identified in WHI.

Emily: You said women were given estrogen who didn't have a uterus, is that right?

Dr. Shifren: That's right. If you didn't have a uterus, you didn't need the Progestin, you received estrogen alone.

Emily: But wouldn't most of the people who didn't have a uterus have had their uterus removed because of some sort of cancer risks, which would have been an estrogen-sensitive cancer[21]. So why would they have been given estrogen?

Dr. Shifren: Women with a history of cancer were not allowed in the study. All of the women that had their uterus removed for benign indication, for a non-cancer indication. To be honest, the majority of hysterectomies performed in this country, especially in that time period, are for benign disease, like bleeding and fibroids.[22]

Emily: The outcome of the women's health initiative did sort of change these recommendations, correct?

---

[19] https://www.drugs.com/ppa/estrogens-conjugated-equine-systemic.html
[20] https://www.drugs.com/medroxyprogesterone.html
[21] https://www.webmd.com/breast-cancer/hormone-sensitive-cancers
[22] https://www.ajog.org/article/S0002-9378(14)02355-2/fulltext

Dr. Shifren: So what happened is when this study was first released to the media, they released the data on the women who took estrogen and progestogen– the women with a uterus– and they released the data on all ages. It's important to realize that the average age of women in WHI was 65[23]. The majority of women who need hormone therapy for treatment for hot flashes are in their early to mid-fifties. So this was not a typical age for women with hot flashes. Because remember, the goal of this study wasn't to see whether hormone therapy treated hot flashes. We already knew that it was to look at whether you could use hormone therapy to reduce the risks of the diseases of aging, particularly heart disease. So you could argue that it was the right study for the question, but unfortunately, all of that information was then placed back on the healthy 50-year-old with bad hot flashes. If you look at the WHI data overall for the women with a uterus who took estrogen plus a progestogen, it shows a slight but real increase in the risk of breast cancer, heart disease, leg, and lung clots and stroke. And that sounds pretty terrifying, but the really good news, if you look at women under age 60 or within 10 years of menopause, there was no increased risk of heart disease and the increased risk of stroke was so small that it's clinically not significant for healthy women under 60. The other good news is that the breast cancer risks increase until four to five years of use. So if a woman started her hormone therapy at 50 and then kind of slowly weaned off and felt well by 55, not only did she not have any increased risk of heart disease or stroke that was clinically significant, she even didn't have that increased risk of breast cancer. Well, we know from other observational studies[24] is that when you give estrogen, not by a pill, but by a patch or a gel or a vaginal ring, you actually don't have an increased risk of leg and lung clots. That's only really seen with oral estrogen. A healthy woman who is within ten years of menopause or under age 60 who has bothersome hot flashes for those women, the benefits of hormone therapy are going to outweigh the risks.

Emily: And so one other question is just, it seems to me like if the people who were in the study were preselected to not have had cancer, but there was an increase in the incidents of cancer within participants, that feels at least intriguing to me that if the average age was 65 a lot of people are getting cancer before 65 right. So if they're not part of the study, but there's an increase of people who get cancer after having been given estrogen.

Dr. Shifren: Yeah, I wouldn't go there, Emily. I don't think it's that relevant. I think basically all older women are at some increased risk for breast cancer and if you go on hormone therapy there is a relative risk of 1.3[25]. It's important

[23] Correction: average age is 63.
[24] https://www.bmj.com/content/364/bmj.k4810
[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1514477/

for real it for women to realize that although you could say, oh that's a 30% increase, that is not a 30% chance of breast cancer. A relative risk[26] of 1.3 for breast cancer is exactly the same as being obese or having two glasses of wine every night. So there are lots of things women do that slightly increase their risk of breast cancer and formal therapy would be one of them, but really right in line with those other risk factors. Women really do need to just sit down with their healthcare provider and make risk-benefit decision for them. The take-home message is that for a healthy woman within 10 years of menopause or under age 60 who has bothersome hot flashes for that woman, it is highly likely that the benefits will far outweigh the risks. We typically encourage women to use the lowest dose that they need for the shortest time that they need. You know, the majority of women come off within four to five years and feel well.

Emily: So it's really this idea of like instead of it being chaotic, you're finding a way to manage it so that it decreases some of these symptoms. But also, I mean I think there is a psychological impact of just not knowing what's going on with your body, right? And that that takes a toll.

Dr. Shifren: So for a perimenopausal woman who undergoing a lot of this reproductive chaos, oh, so it's kind of, I always say it's like adolescence in reverse. You never know what's happening next. Women, for instance, going on birth control pills where they really suppress their own erratic cycles and they get regular doses of an estrogen-progestogen. They treat the bleeding they treat intermittent hot flashes and night sweats. It can be a really terrific way to make it through the menopause transition for women who are menopausal, no longer cycle on their own. those women can receive really much lower doses of estrogen and progestogen really the same levels they would would've been making if their ovaries were still cycling. And those women can have a really nice benefit if they're having hot flashes and night sweats that are disrupting their quality of life. So really when you think of hormone therapy for perimenopause, it's a little different than when you think about it for menopause. But at the end of the day, the take-home messages, the scene, if you're having bothersome perimenopausal or menopausal symptoms, it is highly likely that estrogen will help. And if you're basically healthy, it is likely that the benefits will outweigh the risks.

Emily: It's important to mention that Dr. Shifren was just on a paper published this year[27] that was sort of reevaluating the criteria and the benefits of hormone replacement therapy. She and I kind of alluded to some of the controversy and the history, and I think some people know that there is this reported connection between cancer and hormone replacement therapy. But I

[26] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/relative-risk
[27] https://jamanetwork.com/journals/jama/article-abstract/2735323

thought it was a good time to sort of just take a break and do a little bit of a history lesson on why this is so confusing. So in the 1970s, there was a report that women taking estrogen had increased endometrial cancer[28]. That sort of led to people adding in progesterone[29]. That then led basically to a big epidemiological study, which was done in 1985 that was called the Nurse's Health Initiative[30]. And in that study they found that a third of the women who were taking estrogen had a decrease in heart attacks or cardiac events over women who had never taken estrogen.[31] So it now becomes this thing where everybody thinks taking hormone replacement therapy is probably great. It becomes sort of the standard of care. And then another big epidemiological study is done in the early two thousands, that we've referenced, that's called the Women's Health Initiative. This becomes sort of a hallmark trial because they're looking specifically at how women handle or what the risks are associated with taking hormone replacement therapy. But there are big problems with this study. Starting with the fact that the median age was like 65 years old. So that means that half of the people in the study were over 65 and half of the people in the study were under 65. Well, we know most women going through menopause are going to be under 65 right? And so if you're testing people or you're looking at hormone replacement therapy on people who have already made this transition, it's really not as applicable. But the big findings that were widely reported was that there was an increase in breast cancer with the women who were taking hormone replacement therapy and that risk was reported as of 25% relative risk. And I underscore relative, because I think one of the things that we see more and more today is this idea of statistical significance. And when people are looking at relative risk, they're comparing two groups versus absolute risk[32], which is comparing the total. So to give you an idea of what the breast cancer increased risk was for these women in this study, it was a difference of four in 1000 versus five in 1000 you're talking about one in a thousand increase. But when you turn that into a relative risk, then it looks like a huge number and 25% is scary. Right? So there was a big press conference that was held I, my understanding that they actually held the press conference before they had released the results of the study. They announced that they were halting this trial because all of these women –well, all of these women, we were talking about one in a thousand increase– were developing breast cancer and out of sort of a moral duty, they couldn't continue with the trial. And so that then really set the course where people said hormone replacement is bad, nobody should go on it. You know, were really interested in this because it seems like in terms of quality of life taking hormone

[28] https://www.ncbi.nlm.nih.gov/pubmed/171569
[29] https://www.ncbi.nlm.nih.gov/pubmed/755961
[30] https://www.nurseshealthstudy.org/ Correction: Study, not initiative
[31] https://www.nejm.org/doi/full/10.1056/NEJM198510243131703
[32] https://www.breastcancer.org/risk/understand/abs_v_rel

replacement therapy can help with all of these things, which Dr. Shifren certainly talked about and we talked to them about symptoms last week as well. So I mean I think it's important to mention that that big landmark study that everybody refers to did show statistical significance, but it's not really clinically meaningful. And I think that's a really important thing for people to just sort of think a little bit about, right? Like you don't want to ever do something that's gonna put you at a greater risk for breast cancer. Certainly not. But this risk was so small and it seems like the population of people in the Women's Health Initiative, they were pre-screened so that they didn't have cancer. They also were more likely to be smokers than in the Nurses Health Study. I think it was like 50% of participants had smoked before or were current smokers.[33] A third of them had hypertension. I mean, they're kind of like, they're unhealthy to begin with and it's such a small increase. So I feel like those are really important things. That's where all the controversy came from and now it seems like the medical establishment is, they've picked apart that study and they've realized that it wasn't done properly and that it's probably impossible to say anything conclusive, positive or negative that came out of that study. But that is where the sort of big news is generated from. It oftentimes refers back to that Women's Health Initiative.

Dr. Richardson: My name is Marcie Richardson[34] and I'm an obstetrician gynecologist. I've been taking care of women across the lifespan for 40 years. I got interested in menopause when I entered my forties and have been involved with special care for women with menopause issues for about 20 years. I'm not really an academic, but I do have occasional published articles in particular. We did an article that was in the Annals of Internal Medicine[35] about a year and a half ago having a debate about the use of estrogen to manage menopause symptoms.

Emily: I feel like, you know, talking a little bit about that debate is probably a good place to start because I think the general public is pretty confused about the Women's Health Initiative and the results that came out and is hormone replacement good? Is it not good? Like do you start when you are in your early forties to be like sort of preventative or like, I honestly feel like there's so much confusion about it.

Dr. Richardson: Well, I think there is a lot of confusion and I think part of the issue with the confusion has to do with how complex human biology is. I mean for those of you who don't know the history, estrogen was first proposed

[33] https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.20821
[34] https://www.atriushealth.org/clinicians/martha-richardson-4475
[35] https://annals.org/aim/article-abstract/2671912/should-patient-receive-hormone-therapy-her-menopausal-symptoms-grand-rounds

for women in about 1960[36] and then it was used to treat the symptoms of menopause and to keep women quote "Feminine Forever"[37] unquote. Over the course of subsequent years, we realized that using estrogen alone caused women with a uterus to have an increased incidence of cancer, of the lining of the uterus. So then for women with a uterus, we added progesterone. Then in the 1990s there were a lot of epidemiologic studies that suggested women who were taking hormones were healthier. In particular, they had less heart disease. So there was a period of time when it was advocated for practically everyone. And then they decided really they ought to study that because epidemiological studies are limited by the fact that there are a variety of biases which can always come into observational studies. And the Women's Health Initiative was launched. And after five years, the women on estrogen had more heart disease, more breast cancer, and more clotting problems. So that led to an incredible seat change in the view of estrogen. Many, many women were just stopped on their hormone therapy cold turkey, which was pretty unpleasant for them. As they've continued to look at the data from the Women's Health Initiative, they've come to understand that if women start hormones soon after menopause, that their risk of heart disease is not dramatically increased. And also we think now from epidemiologic studies that women who use transdermal estrogen[38], that is estrogen, that is either in the patch form or a gel or a spray and does not go through the liver initially, that the risk of clotting is greatly mitigated[39]. But we're still uncertain about the role of estrogen for prevention. And I think most people who practice western medicine nowadays aren't using estrogen for prevention. We're mostly using it to treat symptoms and the range of symptoms that women experience with the menopause transition is enormous and often hard to sort out from aging, for instance. I think the great example of that is joint pain and certainly joint pain is a function of aging, but certainly women who experience low estrogen experience increase in joint pain.[40]

Emily: Is that because of bone health?

Dr. Richardson: No, probably it has to do with the lubrication of the joints. It's not the bone health per se. So it is complicated and it's complicated because women are individuals and each of us is different. We have different life histories, we have different genetics and different interactions with hormones. And I think we're trying to sort this out on the basis of population studies, but population studies, you know, in some ways sort of ignore the individual. And the Women's Health Initiative as a great example of why

[36] https://www.amjmed.com/article/S0002-9343(05)00919-8/fulltext
[37] https://www.amazon.com/Feminine-Forever-Robert-Wilson/dp/087131049X
[38] https://www.mayoclinic.org/drugs-supplements/estradiol-transdermal-route/description/drg-20075306
[39] https://insights.ovid.com/article/00042192-201606000-00004
[40] http://www.womenshealth.northwestern.edu/blog/joint-relief-estrogen

population studies fail because they concluded on the basis of the Women's Health Initiative that no one should be on estrogen. In the meantime, the average age of the women in the women's health initiative was 63. So that did an enormous disservice to women who were immediately post-menopause.

Emily: Well, and also isn't the pill have estrogen in it? I mean women are given estrogen.

Dr. Richardson: Yes. But on the other hand, the women who take the pill for the most part are would be making endogenous estrogen. They're making their own estrogen.

Emily: But I've heard of the pill as being something that's often prescribed to women who are perimenopausal and having a hard time.

Dr. Richardson: Yes. Well, the pill is prescribed in perimenopause because the pill turns off a woman's ovaries and it sort of puts the pill in the driver's seat, in the hormonal driver's seat. On the other hand, when you're post-menopausal, you're not making any estrogen. Whereas in perimenopause, your estrogen levels are all over the map.

Emily: Okay. So the pill is okay in that instance as a stabilizer, basically, because the ovaries aren't interacting. That's why the symptoms are turned off?

Dr. Richardson: Sort of, I mean–.

Emily: Tell me why I'm wrong. Please.

Dr. Richardson: So the women, women taking the pill don't have more estrogen than women who are in their reproductive years who are not on the pill. And whereas women using hormone therapy have more estrogen than women who are not on hormone therapy. Does that make sense?

Emily: Sort of. But I guess that from my amateur perspective, what seems logical is that you'd want to kind of have the same amount of estrogen or very gradually be declining the estrogen levels until you get to a point where you don't have any, right? Like I mean that sort of feels like the male model.

Dr. Richardson: Well, I think that's an interesting way of putting it and it's one that I can actually somewhat agree with. For women in perimenopause, their hormones are all over the map. They're up, they're down, they have irregular periods. Using the pill evens out those hormonal ups and downs. Then when the ovaries age out of making any estrogen, the choices are to go off the pill and then you'll have very little estrogen around or you can do a taper plan and you can transition from the pill to hormone therapy and then taper your hormone therapy. It's never been proven whether using hormone therapy alters a woman's menopausal script or not. In other words, if I give you hormone

therapy and put off your hot flashes for five years, then when you stop the hormone therapy, will you just go through the hot flashes only five years later? On the other hand, it's my opinion that if you taper estrogen very slowly that you can modify the hot flashing and menopause experience.

Emily: Dr. Richardson and Dr Schifren have pointed out some clear benefits for women in terms of treating the symptoms. One of the other things that's really interesting is this idea that the underlying health conditions that have to do with cardiac risk, bone health, and brain health might also be sort of an off label benefit of hormone replacement therapy and as Dr Schifren mentioned at the beginning of this episode, it's not something they would ever prescribe hormone replacement for. I think it's really worth mentioning because there's such a tumultuous history of research around hormone replacement therapy that people are, I would say nervous to come out and say anything sort of conclusively about these other health benefits. But what often happens when there's sort of some sort of epidemiological is that people turn to rodent models where they can test and replicate and try and see if they can find any patterns of either risk or benefit for something like hormone replacement therapy. So our next guest is going to talk about his work inducing menopause in mice.[41] We're going to head up to Canada to talk to Professor Glen Pyle.[42]

Glen Pyle: I'm a professor at the University of Guelph in the Department of Biomedical Sciences and I run a lab that looks at heart failure sort of in general. We also look at developing new treatments and we focus on sex differences, not just how it affects women, but also what the differences are between men and women in an attempt to understand the problems and in an attempt to develop new treatments.

Emily: Will you talk to us a little bit about the study that you guys did in mice that was looking at timing of estrogen and progesterone, like sort of hormone replacement therapy? I guess in terms of its relation to coronary heart disease.[43]

Glen Pyle: So we were focusing on the transition into menopause. We know that before menopause, women are relatively protected against cardiovascular disease compared to age-matched men. But that after menopause the risk goes up and or may actually even exceed what we see in men[44]. And so the hypothesis there is that estrogens are protective in women. And that was the basis for hormone replacement therapy. If we put it back in that should be protective, but clinical trials have produced contradictory results, some show

[41] https://onlinelibrary.wiley.com/doi/10.1111/apha.13290
[42] https://graduatestudies.uoguelph.ca/people/glen-pyle
[43] https://my.clevelandclinic.org/health/diseases/16898-coronary-artery-disease
[44] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5993677/

benefit, some don't. And that led us to look at what the changes are that occur in the heart actually during the transition into menopause. And can we develop targets that may be affected to reduce the risk in women and potentially be translated into the men. So we used a a mouse model where we induced menopause in the mice and that allows us to study it in real time. Most models surgically removed the ovaries, so they suddenly go into menopause. And this allowed us to study that transition. And basically what we found was that the heart changes quite significantly during that time, not at a whole heart level. It still appears to function okay. Underneath there appear to be problems.

Emily: So my first question is, how do you induce menopause?

Glen Pyle: Historically, it's been done surgically.[45] You take the ovaries out, and certainly that does happen in some women. That's the vast minority of them. That's how they become menopausal for most women it's a gradual transition where the ovaries over a couple of years– usually about four or five years– reduce the [..] production. So what we did was we used a chemical called 4-Vinylcyclohexene Diepoxide or VCD. And if you inject it into these mice and that's been done at other animals, the ovaries fail over several months.[46] And so that gives us a timeline similar to what we'd see in women where we can watch ovaries fail and watch the impact that has, in our case, on the heart.

Emily: And do mice have similar, I guess like physiological sort of heart hormone interaction to humans?

Glen Pyle: We believe so. It's relatively conserved. There's certainly profound differences between mice and humans. So any study that's done in mice, we don't take it and say, so this is what happens in people. But what it allows us to do is to screen things relatively rapidly. So we're looking at a time course of months rather than years. And we could look at a lot of different things, whereas in human patients we're limited as what we can look at.

Emily: And can you talk to me a little bit about how the heart and estrogen, like how is the estrogen protective or why is that?

Glen Pyle: It does have some effects on cholesterol and metabolism generally overall in the body. So there are those effects that can be beneficial in women. In terms of what it does in the heart, that's actually a black box, which is why hormone replacement therapy has been problematic. Right. We introduced it back into women without knowing exactly how questions work on the heart.

---

[45] https://www.menopause.org/for-women/menopauseflashes/menopause-symptoms-and-treatments/instant-help-for-induced-menopause

[46] https://www.ncbi.nlm.nih.gov/pubmed/22239082

Emily: You mean like the with the women's health initiative that whole–

Glen Pyle: Exactly. Yeah. But not that long ago it was thought that estrogens work by changing gene expression and really over the last 15, 20 years, we know that it actually works in different ways as well. And so we didn't even know how these estrogens work and that's part of what we're actually looking at. What are the targets in the heart? What is it doing? It's a very basic research study.

Emily: Because one of the things that I'm still sort of, I mean like we've done a lot of research about this and we're talking to lots of brilliant people like yourself, but I'm still kind of confused about like this idea that women go from producing estrogen to not producing estrogen and like they're healthy in both of those phases mostly but the transition from one to the other it seems like is where things kind of go haywire. And one researcher had said to us like, it's not that like you like are slowly reducing the amount of estrogen. It's like one month you release a ton of estrogen, like more than you would have normally before you are going through like perimenopause or menopause. And then you like maybe won't produce any the next month. And that she was sort of inferring that it's like the swings that are so hard for women. But I still feel like just from a very logical, not medical background, it feels interesting to me. Right? Like men don't have as much estrogen and they seem to be okay. I mean maybe they're having more heart disease, but it's not, it doesn't seem like it's at the rate. Like, do you understand what I'm sort of getting at? Like it's sort of hard to understand like why is this period around menopause, the hormonal sort of shift is happening if on either side of that shift women are okay,?

Glen Pyle: So first of all, they're right. The decline in estrogens that in that transition are not this gradual decline. They do have these spikes and that's exactly right. It generally goes down over those years. But you see huge spikes up and down. We saw that in our mice. We didn't see changes that gradually changed over time. You know, we would look at one time and it would be way up and then you'd look a little bit later, it'd be way down. And so it was all over the place showing that it's not a linear change. Women have lower rates of cardiovascular disease and generally better outcomes before menopause. After menopause, it does change. So postmenopausal women do not fare as well as premenopausal women. And the risk goes up. Like I said it matches and may even exceed what we see in men. So after menopause, it does actually appear the risk gets worse for women for sure.

Emily: Not worse than men, but worse than their former ourselves essentially.

Glen Pyle: No, it can. So cardiovascular disease is a very broad category. And when you look within that, certainly some problems are worse in women

than they are in men. So, for example, we see a heart attack recovery in the short term being worse in women compared to men,[47] consistent across all different types of cardiovascular disease. And you know, we're not the first, this is not something we've discovered. What works in men does not necessarily work in women and vice versa. But by studying those differences, we can actually make both sexes better. So what is it about estrogens that protects women and can we translate that to men as well as women? And you know, why do women have that increased risk afterwards so that we can try and stop that. You can't just study one sex and apply it to both.

Emily: Right, right. Which I mean, I feel like as historically what has always happened. Talk to me a little bit more about this study and what you guys ended up finding.

Glen Pyle: So we found out a couple of things. If you look at how the heart functions on an organ level, it doesn't seem to change. And that's consistent with what we see in women. If you look at a woman who's, you know, say 49 in premenopausal and then you look at her when she's 51 post-menopausal, the heart's fine. You know, they don't magically go into heart failure. And so we see that in the mice, but when we break apart how the heart functions. That's where we see differences. We need calcium to trigger the muscle contraction[48]. It looks like they need a little bit more as they go through perimenopause. That might seem like a small change. Calcium could actually cause the death of cells if it's in there long enough and at high enough levels. So it might be a small stressor, but one that's there for the rest of their lives. When we look for markers of stress, they were often the hearts. So even though the heart is functioning fine, underneath there was a problem that was stressing it.

Emily: And so what are some markers of stress that you're looking for?

Glen Pyle: So we look for things called cytokines[49], inflammatory cytokines. Some of them are not all of them, but those that go up indicate that there is a stress and an inflammation. Again, a relative small inflammation of the heart. We looked at a signaling molecule called AKT[50], which goes up with a heart stressed and it's tried to compensate and that was turned on, but only at certain times. So that tells us that there's these waves of stress coming and going and the heart's able to compensate. But over the longterm, that may be a problem, which is why we might see increased risk in women.

---

47 https://www.goredforwomen.org/en/about-heart-disease-in-women/latest-research/women-fare-worse-than-men-after-heart-attack

48 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1334730/

49 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2785020/

50 https://www.cell.com/cell/pdf/S0092-8674(17)30413-0.pdf

Emily: And so then how does the hormone replacement therapy help with this? Like reducing stress I imagine, or helping the uptake of calcium. If you could explain that, that'd be great.

Glen Pyle: Yeah. So bottom line is we don't know because we don't know how these estrogens are working in the heart. They have all sorts of effects. Some are good, some are bad. Actually what we did was rather than put estrogens back into the heart– as you would in hormone replacement therapy– we decided to do a more specific approach, which was to target the receptors that the estrogens works through. So there's different types of receptors that we picked two of them and said if we put these back in, what happens rather than just blanket targeting all of them. And that's where we started to see some interesting effects where some of them worked, some of them didn't. And that may eventually lead to a more tailored approach to hormone replacement therapy.

Emily: And so talk to me a little bit about that because I feel like one of the things that was really interesting about your work was this idea of like if you start the hormone replacement therapy, maybe before you really think you need to, it has a longer term benefit because what you're really talking about is sort of like– and excuse this amateur analogy– but it's like wear and tear over time is really maybe the destructive force. Is that accurate?

Glen Pyle: That's fair. And if you can target the problem very early or these changes that occur very early and stop them from occurring, that's a lot easier to slow them down than it is to reverse them. We see that in all sorts of conditions like heart failure. By the time patients present, they're in heart failure. And really the only thing you can do is try and slow it down a little bit. Whereas if we knew early on these patients were in heart failure, we would be much more effective. Now, these women aren't in heart failure, but if they have changes, it's easier to stop those changes very early in the process. And that's what we think would be a more effective approach.

Emily: And so would you consider something like the women's health initiative, which I feel like the average woman out there doesn't really maybe know about the study as much as they know that there was this advice that, you know, hormone replacement therapy is great, and then everybody was told like, well it could kill you. So stop. And now it seems like people have come back around to say, no, actually maybe those results weren't quite the way we had interpreted them.

Glen Pyle: Yeah. So I think that's fair is that there's nothing wrong with the women's health initiative in the standpoint that it's not a bad study. And when I teach this in my class, you know, I talk about these paradoxes and I say it's not that one study was good and one study was bad. They looked at different

things and these different things, while they might be relatively small actually are very impactful. So in the women's health initiative study, they looked generally at older women and women who started their hormone replacement therapy later. When the study was broken down and other studies, what they found was that in general starting hormone replacement therapy, the estrogen replacement therapy early in menopause within a couple of years was more effective than starting it decades later. What we're looking at here is possibly moving that window back and saying as soon as you start to show signs of perimenopause, might that be the most effective time to try and reverse these effects. Cause we see changes that early.

Emily: And in terms of known risks of estrogen, I mean, we know women who have estrogen-sensitive cancers are candidates for this, but are there other things that you feel like are important for people to consider if they're hearing this and they're like, I have a family history of heart disease. Like this is something that's really on my radar. What should they know? The work you're doing is obviously in mice, but it's interesting and you're obviously very aware of what's happening in the field.

Glen Pyle: Yeah, that's absolutely true. We're not trying to minimize any of that and say, no, no, it turns out it's all okay. You don't need to worry about it. Absolutely, there are women like those with this hormone-sensitive cancers that still would be at risk and that's something that they need to along with their physician weigh, like they need to make an informed decision on that. Clearly the translation of the therapy in the men will be problematic because of the sexual side effects. So that's why we're looking at a more targeted approach. Hopefully, by understanding the mechanisms by which risk goes up, we can specifically target that in the hearts of women so that we stay away from breast cancer. So you stay away from uterine cancer if they have a uterus still, if they're not, haven't had a hysterectomy. You know, all those potential negative effects by being much more targeted in the approach. But again, this is very early, so there's not much to change in terms of therapy for women at this moment.

Emily: Yeah. And I feel like there's going to be some crazy Twitter troll who's going to be like, Emily wants all men to be on estrogen. It's like–

Glen Pyle: And we get that feedback too, right? Which is, you know, the misinterpretation is we're saying hormone replacement therapy is good and safe and everybody should take it. And that's not what we're saying. We're saying that we need to understand how menopause impacts the heart better. We need to have a better understanding of women's heart health so that we can either modify this approach or maybe throw it out completely and say, here's a better approach. It's still too early to make those statements and say

all women should be on estrogens or no women should take estrogen is that you can't say that one way or the other. So there's really two points to this study and one is that the therapeutic approach had how can this be translated? I think that's what people are most interested in because they want to see a product in the end that helps women and we certainly understand that. But I think one of the most important things to this is that this is a basic research study and we're asking a question, how does menopause impact the heart? Which if you think about it, it's almost 2020, and we're asking pretty fundamental question about women's heart health that no one has really ever looked at before. That's stunning. If you think about that. This is not a great revelation on our part. We're not the first to think about this, but it's still so underexplored that there's a lot of questions that need to be asked at a very basic level still.

Emily: And is that because that hypothesis hasn't really been put forward before or there's new technology that's gonna to allow you to uncover new answers? I mean I guess I'm sort of trying to understand on this spectrum of information, was this just not really in the purview and if not, how recent is it that people are starting to realize the impact of heart health and women being different maybe because of the actual sort of biological physiological systems of the heart and the interplay of hormones versus the idea of sort of like, well a heart is a heart is a heart.

Glen Pyle: It's actually both. Technically, this approach is new, which is part of the novelty of it, you know, to study menopause in real-time or gradually, so there is that side. We haven't been able to do that. There's certainly been a lot of neglect over the years, which is if it works in men or even if it works in women, although they're underrepresented in trials, it should work in both. Like how much different could a woman's heart be from a man's? Cause when you look at them structurally they look the same or we break them apart, they still function the same way so people have just generally assume it works in one, it works in the other. We've known for quite some time. That's not true. Women respond to some therapies better than men, but also some not as well and that's a problem and no one has really ever decided to look into that and say, well what's the underlying reason for that? Until recently and part of that as a push by governments and funding agencies to say when you design your experiments you need to look at both sexes. Unless there's a reason to only look at one, you need to include both because they don't, the research doesn't translate across both sexes evenly.

Emily: And what got you interested in this?

Glen Pyle: It's actually something that, one of the reasons I got into the research, when I was starting my grad degree, one of the things I was

interested in were estrogens. It was one of the very first things and the sex differences. But when I started in grad school in the mid-nineties I was told that's been answered. That we know estrogens are protective, we know how they work. And so I moved on to other things and have been running sort of a parallel path. And then when I started here at the University of Guelph, we have a number of people who look at sex differences in other systems and was able to talk to them and collaborate on things to try and ask these questions because they're so fundamental. I mean, we're interested in these fundamental questions can eventually lead to translation, but that's why I like to work and this seemed like an area where no one's really working in it. There's a lot of questions to be asked and answered. And so it was a very exciting thing to get into.

Emily: Yeah, I mean, I love to hear that because I think that one of the things that I'm always struck by is this idea of if you go back and you look at like literature, speeches or you know, sort of notes that physicians have taken over the years or researchers doing this kind of work, it's almost like this idea of hormones or menstruation, menopause is like too complicated, right? Like, and it just kind of like messes up the experiment because of all the variables and so like just don't bother with women because men are really stable and easy to test on and I am always like, I get that on one level, but I feel like most scientists want the complex problem, right? Like they want the thing that's harder to understand. It's a bigger problem in a way. Right. Or it's a different kind of problem.

Glen Pyle: There certainly are different variables, but this is actually something that has been pushed up here in Canada. The CHR[51], who's a major health funding agency, has really quashed that idea[52] and said, you know, your excuse for not studying, whether it's female mice or female humans because it's too hard to control things for like the menstrual cycle or something like that is just not true. Yes, there are these variations, but you also have variations like in circadian rhythms.[53] So difference between people at nine in the morning and nine at night. You know, everybody goes through these cycles and you know, we just say, well that's okay, but suddenly something like the menstrual cycle that's too complicated to try and control got and let's just ignore it. It's just not true. And that's bad science.

Emily: So that was a lot to think about this week. But I think it's also really exciting information because I think the more women are getting into these fields and the more that we're recognizing that like some of the symptoms that we experience are really unpleasant and take away from our sense of our

[51] http://www.cihr-irsc.gc.ca/e/193.html
[52] http://www.cihr-irsc.gc.ca/e/51310.html
[53] https://www.nigms.nih.gov/education/pages/factsheet_circadianrhythms.aspx

health span. So I always like to think about things in terms of lifespan, which is the number of years you live. And then health span is like the number of years that you live healthy. If you're experiencing these side effects, they can be really debilitating for women and take away a lot of joy and pleasure of being alive. And so if you think about it that way, then these treatments become really significant in terms of helping women get through this transition. And next week we're going to talk more generally about the menopause transition. So the final stage of not getting a period anymore and what impact that has on your body, how does it make you feel and how does your mind change and what does that new sense of purpose look like? I'm Emily Kumler and that was Empowered Health. Thanks for joining us. Don't forget to check out our website at empoweredhealthshow.com for all the show notes, links to everything that was mentioned in the episode as well as a chance to sign up for our newsletter and get some extra fun tidbits. See you next week.