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### Hormone Replacement Therapy and Heart Disease

You are listening to ReachMD, The Channel for Medical Professionals. Hi, this is Dr. Thomas Bersot, President of the National Lipid Association, and I would like to welcome you to Lipid Lumination, hosted by Dr. Larry Kaskel, and presented by The National Lipid Association. Is the estrogen controversy over? The Women's Health Initiative Hormone trials have been widely interpreted as demonstrating that combined Menopausal Hormone Therapy failed to protect against, and may increase cardiovascular disease in menopausal women. A critical evaluation of the KEEPS trial; however, suggests that the relationship between estrogen and coronary artery disease is unsettled.

Welcome to Lipid Lumination. I am your host Dr. Larry Kaskel. Joining me today is Dr. Elliot Brinton, Director of the Metabolism Section and Cardiovascular Genetics and Associate Professor of the University of Utah School of Medicine and a Fellow of The American Heart Association, and he is going to help us, provide some clarifications on the relationship between estrogen and coronary artery disease.

DR. LARRY KASKEL:

Dr. Brinton, welcome back to Lipid Luminations.

DR. ELLIOT BRINTON:

Thank you very much. It is great to be with you.

DR. LARRY KASKEL:

Well, the Women's Health Initiative was a pretty big randomized trial of Menopausal Hormone Therapy, and it seemed to show quite clearly that Menopausal Hormone Therapy is harmful. Why do you seem to take issue with that?

DR. ELLIOT BRINTON:

Well, that's a good question. I guess part of my problem is my training is in endocrinology and what endocrinologists do for living, is we replace hormones, missing hormones, and occasionally, we'll try to treat a high hormone level. But, most of our job is to replace hormones that are missing and I just don't view estrogen deficiency is being such a terrific thing. I mean, the menopause has certain advantage is for sure, but estrogen deficiency per se has very-very few benefits, and I think a lot of harms. There is a lot of damage done to the body by estrogen deficiency, osteoporosis for example. Crystal clear central nervous system seems to fall apart without

estrogen and atherosclerosis seems to be stimulated by the lack of estrogen. So, I think that in general, hormone deficiency is a bad thing, and so my first reaction is to say, "Hey, let's go ahead and try to replace those hormones. Now the other thing that's really interesting is that Women's Health Initiative, which supposedly shows just a uniform harm across all groups of the population. Actually, there was quite a bit of benefit and that benefit related to any possible harm, in the women who started estrogen prior to age 60. If you think about that for a minute that is what 99% of all clinical estrogen use, so the Women's Health Initiative supposedly showing us exactly what we do in clinical practice. In fact, we are starting a very rare event, which is starting somebody on estrogen for the very first time in their 60's or their 70's.

**DR. LARRY KASKEL:**

So, I mean would you say that there is a universal consensus that continuing Menopausal Hormone Therapy after a few years is necessary to preserve the health of women.

**DR. ELLIOT BRINTON:**

Well, that's the question, and there is something of a consensus, that it is harmful actually to continue (MHT) Menopausal Hormone Therapy after a few years, but the consensus is really not based on anything in particular except just opinion, because the Women's Health Initiative studied the consequences of starting estrogen. Most of the women were not taking estrogen and had never taken estrogen replacement. It showed the consequences of starting estrogen after how many of years, 5, 15, 20, 30 years into the menopause, but it didn't study the consequences of stopping estrogen. So, it's kind of ironic. There are guidelines says where you can take estrogen for a few years if you need for menopausal symptoms, but by God you have to stop it, because The Women's Health Initiative showed that stopping estrogen is so beneficial. Well, they never studied stopping estrogen, so I am really mystified as to how this is so called consensus ever started, because the consensus guideline to stop estrogen is something that the Women's Health initiative didn't study, if any thing the only data we have and these are observational data, they are not very good, are that the sooner you stop estrogen, the more harm is done and the less the benefit, so it's just the exact opposite of which we think.

**DR. LARRY KASKEL:**

So, the common wisdom is usually wrong.

**DR. ELLIOT BRINTON:**

Well, in this case, I don't see any basis for it and it is just a crazy deal. I mean the message was estrogen is bad; therefore we're going to minimize its use. So, I guess, to certain degree that makes sense. But if you look at the detail it's really surprising, that The Women's Health Initiative didn't study anything at all related to what our current guideline say.

**DR. LARRY KASKEL:**

Well, what about the breast cancer, where does hormone therapy cause breast cancer?

**DR. ELLIOT BRINTON:**

Well, it's interesting. They've made a lot about the facts of breast cancer incidents or diagnosis has gone down, since the WHI came out and since there has been a decline in estrogen use. The interesting thing is that, the decline actually started before the publication of the WHI, before there was any downturn in estrogen use, and these effects are so quick, they are kind of too quick. I mean breast cancer takes about 10 or 15 years. I'm not an oncologist, it takes a long time, and so exactly what would quick 6 months' benefit mean, is it just were diagnosing as breast cancer later, we don't really know. If you look at the observational data, which is really all we have, it looks as if taking progesterone and especially with medroxyprogesterone, may indeed increase the risk of breast cancer. But in the Women's Health Initiative, there was a very strong trend towards the decrease in breast cancer, during the first seven years or so at least with estrogen alone, and if you look at the observational data, it probably takes at least 15 or 20 years before there was any discernible rise in breast cancer and at that point in time, all the other benefits, the osteoporosis and what I would use cardiovascular benefits of estrogen in central nervous system etc. prevention of diabetes, it can go on and on, are also great that at 5, 10, 15, 20% increase of breast cancer is probably negligible.

**DR. LARRY KASKEL:**

But this is uncomplicated stuff going on there, and if the doctors don't even understand it, however, we are supposed to have an intelligent conversation with our patients, and what is the primary care physician supposed to do, when a women asks "should I stop or should I continue?"

**DR. ELLIOT BRINTON:**

Well, what I try to do is, to tell a woman what I know and I think, every premenopausal, early menopausal women needs to have a conversation with her provider, and to talk about whether estrogen replacement makes sense or not. Certainly, in the setting of moderate-to-severe menopausal symptoms, I think it is beneficial and very few people argue that that's a bad idea to at least start it and treat temporarily. The question comes out after you have taken it, say for 5 years, your symptoms may be a little better, may be not better the idea is, now you have to stop, and at that point, I think so first of all, would encourage woman to consider estrogen, many of them are scared to take it even though they may need it. Secondly, when she been on it for a few years, I would suggest that she take a long hard look at the pros and cons and if you are taking estrogen plus progesterone especially medroxyprogesterone, there may ultimately be an increase in breast cancer risk, but that can be minimized by reducing the dose of estrogen by considering stopping the progesterone. If a woman is followed carefully, even if she hasn't had a hysterectomy, say dose of 0.3 of Premarin, the risk of uterine cancer is really very, very low and with appropriate follow up with the endometrial ultrasound and what not, the risk is probably zero of developing endometrial cancer. So, if women can be followed carefully, you may not even need the progesterone and if your worry about osteoporosis, Alzheimer disease, any of these other diseases that are diabetes where women who take estrogen have much, much lower rates. I am reluctant to stop the drug and my rule is that I don't stop it unless I have a reason. If a woman develops a complication of estrogen, I will stop it in the absence of a specific indication to stop estrogen, I continue it for life.

**DR. LARRY KASKEL:**

Oh, that is actually very helpful.

If you've just tuned in, you're listening to Lipid Luminations on ReachMD XM160, The Channel for Medical Professionals. I'm Dr. Larry Kaskel and my guest today is Dr. Elliot Brinton, Director of Metabolism Section of Cardiovascular, Genetics and Associate Professor at the University of Utah School of Medicine and a Fellow of the American Heart Association. We are talking about the continuing controversy between estrogen and coronary artery disease.

Dr. Brinton, where do you fall on the topic of whether or not Hormone Therapy can increase the risk of stroke?

**DR. ELLIOT BRINTON:**

Well, there was a trend upward in stroke in the WHI and that's rather concerning, but if you go back to the observational data where we have some dose comparisons, we can see that there is a very different risk of stroke at half dose, so 0.3 of Premarin or it's equivalent say a 0.5 in estradiol. It appears that the risk of stroke may actually be reduced and then they have to do a thrombosis. We know that thrombosis can be caused by estrogen treatment and that's especially true at higher doses and especially true with oral agents. So, if you go to low dose or if you use a patch, the risk of thrombosis is increased very little or may be not at all, and perhaps for that reason there is a suggestion in the literature that low dose may actually reduce stroke instead of increasing it.

**DR. LARRY KASKEL:**

Can you tell me a little bit about the KEEPS trial and how that relates to our discussion?

**DR. ELLIOT BRINTON:**

Well, KEEPS is the Kronos Early Estrogen Progesterone Study, and we are one of the of 9 centers involved in this trial. We're testing something called The Early Start Hypothesis, which is that you use estrogen replacement at a time when estrogen deficiency is just beginning, the estrogen receptors are still there, nothing much has happened, and it appears to have very different effects then if you wait several years, which is what happened on average in the Women's Health Initiative, where the estrogen receptors are either gone or they're greatly altered, you have progression of atherosclerosis. A number of other things and then starting up estrogen all of a sudden, out of the blue, seems to cause a lot of problems. There is an increase in heart attacks that occurs early on, there is this increase in stroke, other things that seemed to happen because you waited so long to start. So, if you replace estrogen at the time of the menopause, it seems to have a different effect, now we don't know this for a fact that is why we're doing KEEPS. We are actually comparing low-dose pill with low-dose patch versus placebo in women that have just entered the menopause. We're to look atherosclerosis in the neck and in the heart and we're going to study a number of other things including breast cancer, breast density, cognition and a number of other things that are of interest with estrogen and see if we can do a better job of looking at this early start, which there was a suggestion in the WHI that that was actually beneficial in those woman we started it early.

**DR. LARRY KASKEL:**

But do you expect that KEEPS will be able to answer whether or not an estrogen patch turns out to be better than giving it by pill?

**DR. ELLIOT BRINTON:**

We may, we may see a difference. We really don't know, because there are so little headon comparison especially randomized trial between those 2 types of agents 2 preparations. My intuition is that they will both probably be helpful. I think there are some women, they prefer a pill versus a patch, some prefer the patch to the pill. They're probably going to be some differences, but my guess is that the majority of the end points will probably be similar between those 2 study arms.

**DR. LARRY KASKEL:**

In addition to pharmaceutical estrogens, we have bio-identical estrogens or plant estrogens. How do you feel about those?

**DR. ELIOT BRINTON:**

I just think it's really a lot of hype frankly, with all due regard to Suzanne Somers and other "experts in the field." It's a marking placing primarily. There are these compounding pharmacies, it'll go and put whatever estrogen you want. The promise is that there is very little monitoring there, the FDA doesn't get involved. They tend to charge more money. The plant estrogens may have effects, may not have effects, they haven't been well studied. I mean on the one hand I always try to go with what my patient's say, if they feel one way or another way on a given preparation I try to accommodate that, but across the board, there is very, very little science behind any of these bio-identical or plant estrogens, and the notion that by, you've given these, that you are automatically protected from any harm that they have been seen in the WHI or other studies. It is really not well founded. So, I think a scientific approach, rationale approach is much better, and this wishful thinking that some alternative estrogen is necessarily better is just not well established.

**DR. LARRY KASKEL:**

And, as we go into the future, by perhaps analyzing individual patient's estrogen receptor, gene polymorphisms, do you think it will be able to tell who'll actually benefit from estrogen and how would it harm?

**DR. ELLIOT BRINTON:**

Clearly, every field of medicine needs that type of answer and I'm sure that there are things we have yet to learn about. The differences between and because 2 women may have totally opposite responses at a number of levels to estrogen. So, we are definitely in need of that type of information. The other thing we need frankly is for the NIH or someone else to sponsor, a discontinuation study. We need to take all these women that we're telling, stop estrogen and say Hey, we are not sure, we'll randomize you, we'll blind you, we'll stop some and not stop others and then follow for 5, 10, 15 years and see what happens. We haven't done that study and that is desperately needed, because we're giving advice basically without knowing what we're doing.

**DR. LARRY KASKEL:**

Dr. Brinton, how do you feel about screening for coronary artery disease at the period of menopause?

**DR. ELLIOT BRINTON:**

I think every woman at the time of menopause needs several different screenings. One of them would be the assessment of risk for cardiovascular disease and sadly, we don't have a really good way of doing this noninvasively. So, what I would suggest is first and foremost start with a lipid panel with assessment of other risk factors such as the presence or absence of diabetes, a hypertension, a family history, all those things need to be looked at carefully and if a statin is warranted for LDL lowering start that because there is excellent evidence of whatever harm might be done by estrogen replacement is reduced greatly by starting a statin ahead of time and certainly one does not replace the other. Now, other things I would definitely look for is risk of osteoporosis. Many of these women need either a heel ultrasound or a DEXA to see exactly how much bone they have. Look at the family history and other risk factors for osteoporosis because making women estrogen deficient by denying their estrogen replacement is guaranteed to lose bone and osteoporosis is a huge cause of death and disability especially among women. Other factors would be family history of breast cancer, although ironically it turns out women with a positive family history of breast cancer are at no greater risk of breast cancer if they take estrogen versus not.

**DR. LARRY KASKEL:**

Well, Dr. Brinton, thank you very much for coming back on the show.

**DR. ELLIOT BRINTON:**

Thank you, I enjoyed it.

**DR. LARRY KASKEL:**

My guest was Dr. Elliot Brinton, Director of The Metabolism Section of Cardiovascular Genetics and Associate Professor at The University of Utah School of Medicine and a Fellow of The American Heart Association and he was helping us understand the controversy between estrogen and coronary artery disease. Thanks for listening.

Thank you for listening to Lipid Luminations, presented by The National Lipid Association. For more information visit ([www.lipid.org](http://www.lipid.org)).