



**National
Multiple Sclerosis
Society**

**MS Learn Online
Feature Presentation
Hormones, Gender, and MS – part one
Nancy Sicotte, M.D.**

Tom>> Welcome to MS Learn Online, I'm Tom Kimball.

Tracey>> And I'm Tracey Kimball. The hormones associated with menses, menopause, and pregnancy can all have an intriguing effect on MS disease activity in women. Researchers are exploring how these gender and hormonal differences may impact the course of MS.

Tom>> Dr. Nancy Sicotte, an associate professor of neurology at the David Geffen School of Medicine at UCLA is working in this area of research. She joins Rick Sommers to tell us what they're learning about the relationship between hormones and MS.

>>Nancy Sicotte: Well, this is work, actually, that a group of us at UCLA who have been involved in, and particularly I want to acknowledge my colleague, Dr. Rhonda Voskuhl, who has really done seminal work in this area, looking at the effect of hormones on the immune system.

And this really comes from a pretty basic observation that's been well known for many years, which is that woman who have multiple sclerosis, when they get pregnant, they experience a decrease in their disease activity during the time they're pregnant. And this is especially prominent during the third trimester, or the last part of pregnancy.

Unfortunately, after delivery there is an increase in disease activity, and what we term a postpartum relapse, and the relapse rate during the postpartum period is increased. And I think that because of that, this beneficial effect during the third trimester was somewhat overlooked.

So, Dr. Voskuhl, being very interested in this really sort of a natural treatment for the disease, which was this pregnancy state, took this observation back into the lab, and then using the animal model of multiple sclerosis, tried to understand what factor that was high during this third trimester of pregnancy could be responsible for this beneficial effect that was seen.

So, with this work she was looking at a variety of hormones that are very high. So, as you know, during pregnancy there are many, many changes that take place. But one of them is that levels of estrogen-like hormones are quite high, so estradiol is high, but there is also a unique hormone that is very high during pregnancy called estriol, and this is a hormone that is made by the fetal placental unit. It is only present during pregnancy, and this seemed like it might be a good candidate as to one of the factors, at least, that was responsible for this improvement in disease activity.

So, from many years of study, it turned that estriol had a beneficial effect on the animal model of MS, and through funding through the MS Society, this led to our clinical trial -- two clinical trials, actually, but we did a pilot study. So, for the first time we used this hormone, estriol, to treat women who had multiple sclerosis, to see if it had a beneficial effect on disease activity.

We are now in the process of doing a multicenter, double-blind trial where we're giving estriol or placebo in combination with Copaxone to 140 patients in multiple centers throughout the United States. And this study is a two-year treatment trial, and we'll be looking at relapse rate as our readout, and this is really the first time that a hormonal treatment has been

tried in a double-blind study such as this for autoimmune disease and certainly the first time it's been tried in multiple sclerosis.

>>**Rick Sommers:** I'm curious, along those lines, because I know that women who are pregnant, and obviously I am not one, have to protect their bodies as they go through pregnancy. So, certain medical testing may be off limits at a certain point. Do they do MRIs at that stage, and were there any noticeable differences on lesion activity?

>>**Nancy Sicotte:** So, that's a great question, and there is very limited data on MRI activity. But what we do have very good data on is relapse activity. So, in general, certain MRI characteristics are associated with in relapse activity. That would be new active lesions, gadolinium-enhancing lesions, new T2 lesions.

During pregnancy it's actually not safe to use gadolinium, so our measures of disease activity are a little bit limited, because gadolinium is really the best marker of acute disease activity. But there have been a few studies, very few studies that have looked at disease activity during pregnancy and then compared it to disease activity during the postpartum time.

But I think what we really have focused on is looking at the relapse rate, because ultimately, I think, while MRI activity is a useful surrogate marker in some ways, it's really the clinical activity that is most important.

So, I think it's been very nice to be able to now have information and data to tell patients, this is what you should expect. There is evidence that pregnancy in the long-term is certainly not detrimental to disease progression, and there is some limited data that it actually may be beneficial, pregnancy.

So, what I tend to tell my patients is, I counsel them to think about the pregnancy period as extending over the entire year. And so there will be fluctuations and disease activity that are fairly predictable, so that during

the third trimester, for example, disease activity will be low, but that during the postpartum time, this is an area or a time when they would be more likely to have relapses. But if you look at the whole year, disease activity, if you average it over the year, has not really changed for most patients.

>> **Rick Sommers:** Okay. You know, we're talking about the fluctuation of hormones during pregnancy. How about during menstruation and menopause?

>> **Nancy Sicotte:** So, menopause, there is relatively little data available, and I think a really under-studied area in MS. I think within the clinical community there's a sense that disease activity tends to taper off during the menopause and after menopause. I've heard some clinicians say that they stop disease-modifying therapies after menopause.

But the reality is, it has not been studied in a rigorous way, and there are definitely reports that women with MS report a worsening of their symptoms around the time of menopause. And, again, not disease activity, per se, but other complaints that may be magnified, normal complaints at that time, such as cognitive problems, mood changes, mood swings, and so on, that may be exacerbated -- that's probably not the right word -- but may be magnified during this time of transition in women who have MS.

>> **Rick Sommers:** Which are normal menopausal symptoms, so-to-speak.

>> **Nancy Sicotte:** Exactly. But in terms of what's happening with the immune response and how that might be worsened or even made better by this transition, there's very little data on that. And I think that would be an area of very fruitful work, potentially.

So, there is a lot of evidence that many neurological problems are worsened around the time of menses, and this includes MS symptoms. So, in general, patients with MS will report that they have an increase in their

symptoms right before or at the time of their menses. And this is undoubtedly related to all of the changes that take place around menstruation, including a rapid drop in estrogen as well as progesterone. And so these will cause neurological symptoms to worsen, just like migraines are increased around that time, seizure activity. Some women only have seizures around that time because of these -- I think it's mainly this fluctuation, where you have these rapid changes in hormone levels that lead to that.

In terms of relapses or new disease activity, there is no evidence that the menstrual cycle itself is a risk factor associated with increased new inflammatory activity. But certainly patients feel much more symptomatic around that time. For example, fatigue, which is for women who don't have MS, is a common menstrual or perimenstrual symptom, and in MS patients who have an underlying fatigue, it may just be magnified because of that.

Tracey>> I appreciate Dr. Sicotte's insight, it's exciting to hear that new MS therapies may be introduced through the research on hormones.

Tom>> I look forward to part two of Dr. Sicotte's interview when we'll hear more about the possible beneficial effects that testosterone may have for men with MS.

Tracey>> We'll see you soon.