Pregnancy and a Rare Neuroimmune Diagnosis

You can view this presentation at: youtu.be/rVzBolCna9s

[00:00:00] **Roberta Pesce:** Our next talk will focus on pregnancy and rare neuroimmune disorders, including family planning following a rare neuroimmune diagnosis. What medications are safe and unsafe during pregnancy, and how pregnancy can affect the symptoms for a rare neuroimmune disorder. I'm joined today by Dr. Tanuja Chitnis. Professor of neurology at Harvard Medical School, and Senior Neurologist at Brigham and Women's Hospital and Massachusetts General Hospital. Dr. Chitnis, welcome and thank you for being here, the floor is yours.

[00:00:38] **Dr. Tanuja Chitnis:** Thank you, it's my pleasure to be here, Roberta, and I'd like to thank the RNDS for the invitation to speak. So, I'm just going to advance my slides, and I can see that we did advance. So, the questions that I'd like to tackle today is number one, what are the pregnancy effects on neuroimmune disease. Number two, does neuroimmune disease have an effect on pregnancy itself? Number three, questions about delivery and breast feeding, and number four, treatment considerations for pregnancy and baby.

[00:01:09] So I'd like to go ahead and move onto our first set of topics, and just as a little bit of a background, I think we all know that autoimmune diseases, and especially neuroimmune diseases have been increasing over the past 5 decades, and this is just a snapshot, and we also know that females are more likely to be affected by most autoimmune diseases. This is not true for every disease, but in many cases, and especially neuroimmune diseases there are a number of women in a very high female-to-male ratio. So, what does that mean in terms of thinking about hormones and pregnancy, and just to also give you a little bit of background.

[00:01:51] So we do know that estrogen and testosterone have different effects when it comes to inflammation as well as effects on the nervous system, called neuroprotection or neurodegeneration. And in general, estrogen at what we call cycling ranges, or estradiol, can be pro-inflammatory. And you see this arrow right here that says it increases more inflammation with normal levels of estradiol. In pregnancy, as a sort of difference, there is a higher, much higher ranges of estrogen species including estriol, and that's the predominant form in pregnancy, and that tends to be anti-inflammatory, and the levels of estriol and estradiol are much higher in pregnancies than compared to a normal cycling state.

[00:02:40] In contrast, testosterone is actually anti-inflammatory, so that's why in part for most of these males are less likely to be affected by autoimmune and neuroimmune diseases. And then neurodegeneration, there

is a protective effect for both, and maybe particularly for higher doses of estrogen. So I think one thing that's very important for any woman to consider when they have a neuroimmune disorder is whether or not they are interested in conceiving or desire to have a family in the next few years, and this is an important discussion point to have with your neurologist, with all of your doctors, so that they're aware of your potential plans or interests, and also timeline, and if it's not right now you might be thinking about it 3 or 4 years down the road, but I think that's important to ensure that your doctor is aware of that factor so that they can help you to start planning for pregnancy.

[00:03:39] So especially many younger people are affected by neuroimmune diseases, and especially during their reproductive years, and it's key in managing pregnancy and planning for pregnancy early on, and this includes both discussions around reliable contraception as well as fertility and conception planning, and then all the other topics around pregnancy, postpartum care, breastfeeding and coping with parenting. And of course, thinking about a disease modifying therapy is also central to this discussion, since it can affect many of these aspects. So, if you are considering pregnancy, the general recommendation is a referral to a higher risk obstetrician, who will work with you and your neurologist, as well as any other doctors who are a part of your care, and it could be your urologist, or other providers.

[00:04:32] If there's not a high-risk OB in your area, at least an obstetrician who is familiar with the disease that you have and is in communication with your treating neurologist. It's very important to think about medication timing and stopping, which might be planned ahead of the time that you try to conceive, as this could have effects on the longer-term outcomes. And in general, if you are having challenges with conceiving within about six months, then you might consider a consultation with an artificial reproductive treatment specialist, in order to determine if there could be a biological reason for this delay, and also to help move the process along so that you might not be off disease modifying treatment for a longer than needed period of time.

[00:05:26] So the first question that I'll work on, or we'll talk about is the effect of pregnancy on the course of neuroimmune diseases. And what we do know comes in part from the multiple sclerosis literature, which has now shown fairly consistently that during pregnancy, and I have divided this into trimesters, but especially during the third trimester, and maybe even just before, there seems to be a decrease in relapse rate during that third trimester. So, between months, typically six to nine or five to eight there's a decrease in relapse rate.

[00:06:03] However, what is also very apparent is that there is an increase in relapse rate in multiple sclerosis after delivery. And remember, these hormones that were somewhat protective, the estrogens, they decrease quite dramatically after delivery, and that might be the reason for increased relapses. Progesterone also decreases quite rapidly. So, this has also been now shown in NMOSD, and what we do know from fairly large studies in NMOSD, that we don't see that dramatic protective effect in the third trimester as in multiple sclerosis. We don't also see an increase in relapse rates in NMOSD during pregnancy, which is generally good news. However, we do see this increase in relapse rates after delivery, during the first three months in particular, and maybe even up to 4 or 5 months.

[00:07:00] So again, the role of hormones plays a key role here, and the drop in estrogens and progesterone are probably likely culprits, so this is a period of time postpartum, post-delivery, to be thinking about restarting disease modifying treatment if you are at risk for relapses, and this may or may not be every case, and some factors to consider are pre-treatment or pre-pregnancy relapse rates, how difficult it's been to control your NMOSD and other factors. And this is just another slide showing across different studies also consistently showing after delivery this increased relapse rate post-delivery or postpartum.

[00:07:44] Now what about MOGAD and double-seronegative NMOSD? So, what we have seen from relatively large studies, but these are rare diseases, of course, that there is also an increase in relapse rate in MOG

antibody associated disease, as well as in the double-seronegative, and it might be even more prolonged in the double- seronegative patients. But again, these are small numbers. So, this is postpartum there seems to be an increased relapse rate, both in MOGAD and in double-seronegative NMOSD around months 0 to 4 or 5 after delivery. So that seems to be a key period to consider restarting medication. So just to summarize this section, so the effect of pregnancy on the course of neuroimmune diseases, most neuroimmune diseases are associated with an increased relapse rate in the 3 months after delivery, and this is a time to consider restarting DMT, which stands for disease modifying treatment, or considering a course of steroids.

[00:08:47] Now of course all of this has an impact on breastfeeding, which we will discuss in a few slides. So, topic number two is the effect of neuroimmune disease on pregnancy itself, and what we know is that pregnancy itself is a state in which your body changes dramatically. There are new blood vessels which are forming between the placenta, the maternal portion of the placenta, the fetal portion of the placenta, and there are also immune cells which are helping the mother's body to not reject the baby because of immune differences, and all of these come into play in some neuroimmune disorders.

[00:09:27] So the question at hand is, is neuroimmune disease associated with pregnancy complications? And the short answer is with MS we don't see an increase in complication rate, in Neuromyelitis Spectrum Disorder, especially aquaporin-4 positive disease, there have been reports of higher rates of miscarriage and pre-eclampsia, which seem to be due to this interaction of immune cells as well as the vascular changes that are occurring in pregnancy. And in MOGAD and double-seronegative patients, we don't have enough data.

[00:10:01] So in NMOSD, the studies that we do have reported a slightly higher increase rate in miscarriage, and this study was 12.9 percent in patients with NMOSD. The rate of something called pre-eclampsia, which is associated with high blood pressure, even liver function test changes or liver changes was also higher in NMOSD compared to the general population. So those are indeed very important risks to be monitoring during pregnancy, and this is what requires a referral to a high-risk obstetrician who is aware of the management of these conditions, or a very experienced obstetrician who is also aware. So, this has also been worn out in large studies fairly consistently showing that the rates of spontaneous miscarriage or abortion are higher in NMOSD. And part of the reason is that aquaporin-4, which is the target of NMOSD, in large part is expressed in the placenta. And so there may be an immune reaction occurring, especially during the second trimester, and this has been associated with inflammation in the placenta, and areas of necrosis, as shown in this one case.

[00:11:21] So again, very important to be under the care of an experienced obstetrician. So as a brief summary to this section, aquaporin-4 antibody positive NMOSD is associated with an increased risk of miscarriage and pre-eclampsia, and it's unclear at this point if medication changes these risks.

[00:11:41] So what about the effect of treatment on pregnancy and baby? So, the question is will I relapse if I stop disease modifying treatment prior to or at pregnancy? And so, one must consider age, and in many cases, there may be younger ages associated with a higher likelihood to relapse, and therefore continuing or considering discontinuation in younger age might be a concern. Considering prior disease activity, relapse rates and other factors relating to the specific disease modifying treatment, or DMT, that you're on. And these are all things like half-life and pharmacokinetics and the risk of rebound disease activity. So, this is a very long discussion to consider with your neurologist.

[00:12:31] The other decision point is will a treatment harm my pregnancy or baby? And at this point the available data is largely observational. There are data from some other disease conditions for which some of the DMTs have been used, such as rituximab, and there are ongoing pregnancy registries, especially for most of the recently approved FDA medications, and this is very important to consider participating in, or helping with, because we can only learn through pregnancy registries and research studies.

[00:13:05] So the risk benefit ratio is something we must really weigh very carefully, and it's important to also understand the general population risk of things happening during pregnancy, including spontaneous abortions, which range from 10 percent to 20 percent. So, this is unintended miscarriages, and they do occur unfortunately, and the range in otherwise healthy women is 10 to 20 percent. The general population risk of fetal malformations Is 2 to 4 percent, so that's another factor to consider as a background. So not every issue that occurs may be due to medication, it just may be due to chance.

[00:13:45] So what do we know about disease modifying treatments prior to conception? So, in general what I counsel my patients on is we should have a discussion around your risk of relapsing, whether it's appropriate to stop treatment, and then which treatment you're on. And there I think the discussion around trying to optimize pregnancy or conception is important, so if you're trying to conceive, consider basal temperature measurements, charting, ovulation kits, and other factors. So also consider stabilizing active patients, or if you're very active with alternative therapies before initiating or conceiving. And in some patients, if they're trying to conceive and we know that they may be active, I give monthly IV steroids. One dose, around the time of menses or at the time of menses, because we know you're not pregnant at that point, and therefore then we can have some protection in place.

[00:14:49] So in terms of medications, we used to have FDA pregnancy categories A, B, C and D and X. So obviously X is ones that have been associated with teratogenicity or serious adverse events, and category A are those medications which have had large controlled human studies, and this is somewhat rare, just given the rarity of many diseases and treatments. And then the others fall in-between. Now recently the FDA has shifted to full pregnancy disclosures, and if you read the product insert then there will be a full disclosure of all the risks that have been observed to date, including risks to the mother or embryo and fetal risks, and that will help you and your providers to decide on timing or discontinuation of treatments.

[00:15:40] Another thing to keep in mind is that treatments differ in how they're transported into the placenta. So monoclonal antibodies are actively transported during the second trimester, and small molecules have variable transport. Rituximab in pregnancy has been used, and this is data from observational studies, and in 102 pregnancies, there were 78 lives births and 12 spontaneous abortions, which is within the range of what we expect. The factors that were noted that in the children, in the babies when the B cell counts were checked they were low in 39 percent of newborns, but these did normalize within 6 months. So, your newborn, your baby might have lower B cell counts, but it does seem to normalize, and I think this is weighing the risk benefit ratio of whether it's appropriate to be on rituximab during pregnancy. Some providers will dose it 3 months prior to conception with the hopes that the B cells will be suppressed, and this is a reasonable balance for both mother and baby.

[00:16:48] Ocrelizumab has been approved for forms of relapsing MS, and is also used in other disease forms, and the half-life is slightly longer than rituximab. And an observational study of 81 pregnancies, 22 had a known outcomes and some pregnancies were terminated electively. Of the known outcomes, eight resulted in healthy babies and one infant with trisomy 21, or down syndrome was observed. And so, you can see that these are small numbers and small studies. Tocilizumab in pregnancy, there seems to be a slightly increased risk of miscarriage and pre-term birth and a 12-month washout is recommended.

[00:17:28] In terms of newer medications, satralizumab may be similar to tocilizumab, but more data is needed. And eculizumab has been shown to be safe and effective for pregnancy in the condition of paroxysmal nocturnal hemoglobinuria, which is another condition that has been treated with eculizumab. So, we don't know yet about NMOSD, which of course, eculizumab is used in, but we are looking for more data. Steroid use is something that providers often consider during pregnancy, and the rules around steroids is that we've talked about prophylaxis, but it's better to not administer steroids during the first trimester because there is

a risk of possible cleft lip to the baby, to the fetus. And the second and third trimester if steroids are needed there's a possible risk of increased birth weight, but it's thought to be fairly safe.

[00:18:27] There are different forms of steroids, and prednisone, prednisolone, and methylprednisolone, less than 10 percent reaches the fetus, so those are generally considered the safer forms. In contrast, these two forms, betamethasone and dexamethasone do cross into the placenta with minimal metabolism, so these should be avoided. And IVIG is generally safe for use during pregnancy and might provide some benefit in various conditions. In terms of vitamin D, so in general, course pregnancy prenatal vitamins are recommended, but vitamin D itself might also be protective for fetal outcomes for risk of multiple sclerosis. We don't know about other neuroimmune disorders yet. So, to summarize this section, we've talked a bit about NMO pregnancy recommendations and monitoring, immunosuppression, and pregnancy management.

[00:19:22] So a quick summary on questions around delivery and breastfeeding. So, the method of labor and delivery should not be impacted by the disease. If you do have weakness in the lower extremities, in the pelvic floor, then, only then a cesarean section might considered, and in general at least from what we know in multiple sclerosis, epidural anesthesia or general anesthesia seems to have no effect on the course of pregnancy or in women with MS. This is likely true for other neuroimmune disorders, and we might consider stress dose steroids if there has been an extended exposure to corticosteroids in pregnancy or prior. So, breastfeeding, in some studies for multiple sclerosis there has been some evidence that exclusive breastfeeding, so the baby receives no bottle, no formula, might be protective for relapses, post-delivery, so postpartum. However, we don't know about other neuroimmune diseases.

[00:20:26] During breastfeeding if one needs to have steroids if there is a relapse or new symptoms, then in general it's better to wait at least 1 or ideally 4 hours after the dose of steroids before breastfeeding. And what I generally tell my patients is to pump and dump on the day of a steroid infusion, and then you can go ahead to breastfeeding, and so this is where stored milk might be important to consider. So, there are some recommendations for disease modifying therapies in breastfeeding for women with MS, and some of these are common drugs to other neuroimmune diseases, and we're still learning about some of the antibodies, and whether they do penetrate into the breast milk, and there's more data to come.

[00:21:16] So just as a quick summary in terms of postpartum management. So, consider the risk of not going back on disease modifying therapy, versus the risk of other issues, and then we can consider postpartum IV steroids with these rules in mind. And also, another factor to monitor for after delivery is postpartum depression, which is a very real condition, and all women need support, and this should also be monitored for. So, to summarize the talk, I think the key messages here are to plan for pregnancy, consider who your team is, and make sure your team is communicating with one another, treatment considerations, and please consider contributing to research. Thank you very much for your attention.

[00:22:10] **Roberta Pesce:** Thank you so much, Dr. Chitnis, for this very informative talk. We've received some questions from our community, and some of them have been answered already within your talk. Unfortunately, I don't think we have time to cover them all, but we will make sure to reach out to you and ask them, and we'll get back to our community members about that. So, thank you very much for your time.

[00:22:33] **Dr. Tanuja Chitnis:** Thank you.