

# NMOSD and Pregnancy/Family Planning

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**Intro:** [00:02] ABCs of NMOSD is an education podcast series to share knowledge about Neuromyelitis Optica Spectrum Disorder or NMOSD. A rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerves and spinal cord. ABCs of NMOSD podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association, and in collaboration with the Sumaira Foundation for NMO and Guthy-Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

**Dr. GG deFiebre:** [00:59] Hello and welcome to the ABCs of NMOSD podcast series. Today's podcast is titled "NMOSD and Pregnancy/Family Planning." My name is GG deFiebre, Director of Research and Programs with the Siegel Rare Neuroimmune Association. ABCs of NMOSD is made possible through a patient education grant from Horizon Therapeutics. Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

**Dr. GG deFiebre:** [01:36] For this podcast we are pleased to be joined by Dr. Tamara Kaplan and Dr. Anastasia Vishnevetsky. Dr. Kaplan is an Assistant Professor at Harvard Medical School. She is also a board-certified neurologist and multiple sclerosis/NMOSD specialist at Brigham and Women's Hospital in Boston. Dr. Kaplan obtained her medical degree at the University of Pennsylvania School of Medicine in Philadelphia. She completed her residency at the Harvard joint program with Brigham and Women's Hospital and Massachusetts General Hospital. Dr. Kaplan finished her training with a fellowship in multiple sclerosis and neuroimmunology at the Brigham and Women's Hospital. Dr. Vishnevetsky is a Neuroimmunology fellow at the Brigham Mass General MS and Neuroimmunology Fellowship program. She graduated from the Mass General Brigham Neurology residency and completed her internship at Brigham and Women's Hospital. She has recently been awarded the Sylvia Lawry Clinical Research Fellowship, as well as the NeuroNext Clinical Trials Fellowship, and is currently focusing on clinical trials addressing symptomatic aspects of demyelinating diseases such as fatigue, pain, and spasticity. Thank you both so much for joining us today to talk about NMOSD and pregnancy. We're going to go through a few questions about this particular topic. So, to start Dr. Vishnevetsky, do you mind just telling us how NMOSD impacts fertility?

**Dr. Anastasia Vishnevetsky:** [03:00] Yeah, absolutely. So, we don't really have great data on how NMOSD affects fertility per se, but it does seem like NMOSD activity and relapses seem to increase the risk of miscarriages. We do know that the aquaporin-4 channel is expressed at pretty high levels in the placenta. So that makes sense. We don't really know if this applies to seronegative NMOSD patients and MOG positive patients as well. But increased aquaporin-4 positive NMOSD activity increases the risk of miscarriages and then having multiple autoimmune conditions is pretty common in individuals with NMOSD as well. And those two combined seem to increase the risk for preeclampsia as well. But we don't really have great data about fertility and that might be something that we'll find out more about in the future.

**Dr. Tamara Bockow Kaplan:** [03:52] Yeah, and I'll just add to you know the data about preeclampsia. Actually, we were going back and forth about whether or not we really did think NMOSD impacted the risk of preeclampsia. And I think really the data is unclear because as was mentioned it seems that you know there was a case series that showed that women with NMOSD did seem to have higher rates of preeclampsia than those who did not. But those women also had other comorbid autoimmune diseases. So, we're still awaiting more conclusive data.

**Dr. GG deFiebre:** [04:33] Yeah. Absolutely. Got it. Thank you. And so, then Dr. Kaplan, what should someone with NMOSD know about contraception or birth control or family planning?

**Dr. Tamara Bockow Kaplan:** [04:45] Yeah. I mean I think the first thing to say to start out by saying is patients and their neurologists should discuss family planning and especially if a patient is intending to become pregnant within the next year. This is a really important conversation to have with your neurologist because it can guide your healthcare provider in the treatment and in the care plan. And you know, there are certain medications in which it might be important to use contraception because they can be teratogenic which means they can potentially cause birth defects. But truly any form of contraception is safe in NMOSD patients. And so, the goal should be to use highly effective contraception that's easy to adhere to and that's something different for different people. Some people prefer a pill, some people prefer an IUD but another thing to keep in mind is that women who are using hormonal contraception like a birth control pill and are hoping to discontinue their NMOSD treatment before conceiving may be advised to discontinue the hormonal contraception first and allow for return of their normal ovarian cycle and use barrier methods in the meantime, before discontinuing their NMOSD treatment. And the idea there is to reduce or minimize the time off therapy and sometimes it can be really helpful to do all of this with a reproductive endocrinologist to help optimize chances of conception.

**Dr. GG deFiebre:** [06:29] Great, thank you for that overview and certainly an important discussion to have with someone's health care providers. So, then Dr. Vishnevetsky is there kind of considerations around how the timing of someone's most recent relapse might influence when they should try to conceive?

**Dr. Anastasia Vishnevetsky:** [06:49] Yeah, absolutely. So, the big picture is that intrapartum and postpartum outcomes in patients with NMOSD are closely linked to disease stability for the year preceding pregnancy. Although ultimately the timing of conception is a really personal decision. There's a lot of health-related factors and personal factors that should be taken into account. But in terms of the data and the guidance we can provide and how NMOSD might play into that. One study that looked at miscarriage rates found a higher risk of miscarriage and those would have a relapse within the nine months prior to conception or during the pregnancy, even beyond the miscarriage rates, pregnancy is just a generally difficult time on the body. And so, during the active recovery phase from a relapse when you're trying to do rehab and trying to just get back to, you know, the best functional status that you can, that might be a difficult time for pregnancy as well. Just a note about miscarriages, a bit about miscarriage rates already, you know, miscarriage rates in the general population are a lot higher than most people realize. And so, you know, these increases in miscarriage risk are still you know, still relatively small or moderate in size compared to the baseline risk and other aspects that can influence someone's health.

**Dr. Tamara Bockow Kaplan:** [08:16] And I just want to add. You know, I should have mentioned this from the beginning, but just I mean, I think some people have this misconception that people with NMOSD shouldn't get pregnant and shouldn't conceive and that's not true. But as Anastasia is saying, you know, I think it is important to make sure that your NMOSD is under good control, that your disease activity is under good control before you proceed to that next step.

**Dr. GG deFiebre:** [08:45] So tell me what needs to be considered before someone becomes pregnant if they have NMOSD for example whether medications as you know are teratogenic or can cause issues in pregnancy?

**Dr. Tamara Bockow Kaplan:** [09:00] Yeah, I mean this is a really good question and I hope we have time to talk about this in more depth. But there are a few medications that are used to treat NMOSD that we know are not safe in pregnancy and those include mycophenolate, methotrexate, mitoxantrone and even the steroid dexamethasone. You know, if we're choosing how to treat people with steroids, we know that prednisone and methylprednisolone are much safer than dexamethasone. And that has to do with that steroids ability to cross the placenta. And so, you know, if someone is considering pregnancy, it's important to switch to a safer medication like azathioprine or some of the monoclonal antibodies which we're gonna talk about in a little bit.

**Dr. GG deFiebre:** [09:50] Sounds good, thank you. And then we've talked a little bit about relapses. But Anastasia is there a risk of relapse during pregnancy itself?

**Dr. Anastasia Vishnevetsky:** [10:01] Yeah, absolutely. So there seems to be a roughly stable to maybe even slightly increased risk of relapse during pregnancy with NMOSD that's different from the case with multiple sclerosis where there is a decreased risk of relapse and even a stabilization of disease activity during pregnancy. So NMOSD seems to be roughly similar to what it was like before pregnancy. A lot of this data is coming from before patients were on as effective therapy as they're on now when relapses are really reduced. The other thing is that relapse risk increases sharply in the early postpartum period. And there are quite a few studies corroborating that. I think an important piece of kind of combining both of those is that it's important to try to stay on some kind of therapy, if possible, to reduce the risk of relapses. And in particular have a good treatment plan before pregnancy or during pregnancy about what we're going to do to protect the mother from a relapse right after pregnancy.

**Dr. Tamara Bockow Kaplan:** [11:10] And that's actually just such a good point because you know, what sometimes happens is that people choose to stop therapy and then hope to conceive and you know, a lot of these oral medications, the half-life is very short and it's out of your body pretty soon after you stop it. And then, you know, I mean not everyone conceives the first time they try for many women it can take six months or even a year. And so, you know we want to minimize the time off treatment and maximize the time that the mom is protected. And you know thinking about which therapy we choose can be really important in that discussion.

**Dr. Anastasia Vishnevetsky:** [11:53] And I think a lot of the data that we have some of the earlier data that's showing this all these increased relapse risks during pregnancy and afterwards also stem from treatment decisions that were made in the past where you know, we didn't know about how safe medications would be during therapy. We didn't know how significant the consequences would be of stopping therapy. And so, a lot of patients tended to be more off therapy in the postpartum period.

**Dr. Tamara Bockow Kaplan:** [12:25] And you know also just add to that. It can be really helpful to work with a reproductive endocrinologist and I actually work quite closely with a reproductive endocrinologist for a lot of my patients. And you know many, I mean for a lot of people it can take up to a year to get to see a doctor like that. But in the case of NMO or multiple sclerosis, it's much easier to get to see someone sooner. And those types of doctors can help really optimize the chances of conception and as I tell so many of my patients when you decide you want to have a baby. There's nothing romantic about getting pregnant. You just, let's just get it done. And there's so many ways now to help in that process. Things like IUI and you know timing of ovulation and that sort of thing. So, you know a lot of people assume that reproductive endocrinology means IVF and that's not necessarily the case. It's just about maximizing the chances.

**Dr. GG deFiebre:** [13:38] Got it. And so, Anastasia mentioned that you know obviously the idea is to have someone on medication if they have NMOSD to prevent relapses because of the risk of relapse. So, Tammy are current NMOSD disease modifying medications safe for pregnant patients?

**Dr. Tamara Bockow Kaplan:** [13:57] Yeah. So, you know just to reiterate, let's start with the ones that we know are unsafe, and that includes methotrexate, mycophenolate, and tacrolimus. And I think I mentioned mitoxantrone also, but medications that have shown some reassuring data include azathioprine and rituximab. And we can extrapolate that to think about inebilizumab and also eculizumab. And you know one of the advantages of using these monoclonal antibodies like these anti-CD20 therapies for example is we know that the effect of the drug lasts at least six months if not longer. And so oftentimes what I'll do with one of my patients is allow them to get that rituximab infusion and then you know maybe two months after that infusion they can start trying to conceive. And you know when they do conceive, they're still protected, you know, within that whole first trimester of pregnancy.

**Dr. Tamara Bockow Kaplan:** [15:09] And then people ask the question well is rituximab safe during pregnancy. And the first thing to say is, you know, we can talk, we're gonna talk about that I hope in a little bit more detail. But people often worry about does this drug cross the placenta and for the first 12 weeks of pregnancy, you don't have a placenta. You know, and the unborn fetus is about the size of the poppy seed for a long time. And so, you know, I don't think that's a concern. And the half-life of the drug is such that it's completely eliminated from your body by about 16-18 weeks. So, if you get it two months before you conceive, then by the end of your first trimester you have no drug at all in your body.

**Dr. Tamara Bockow Kaplan:** [16:01] That being said, even if you did have rituximab in your bloodstream, there's a lot of really reassuring data from case series that we've seen even from the rheumatology literature and even in women who received rituximab infusion in the third trimester of pregnancy. The major and only side effect that was seen was that the babies were transparently born with low B cell counts that spontaneously recovered within six weeks. So, is that a concern? You know, I mean it's not, the important thing is it's not causing any birth defects that we've seen at all. But whether that's a concern about babies' ability to respond to vaccines, that's another question. But we're not even talking about necessarily infusing people during their third trimester. Eculizumab has also shown some really reassuring safety data from its use in PNH. And it seems to be safe to use throughout pregnancy. And there's no reason why we can't extrapolate that data to think about NMOSD patients as well.

**Dr. Anastasia Vishnevetsky:** [17:19] Yeah. And just to kind of piggyback on that, I kind of just group the medications that I would use during pregnancy into kind of this anti-CD20 blocking therapies which are rituximab and then in MS we use ocrelizumab and then very closely related to them is inebilizumab. So, all three of those medications essentially deplete our B cells, a specific type of B cell and they're all three of those medications have pretty much the same dosing scheme where they're dosed every six months and then you can monitor them and monitor the activity of the immunotherapy by measuring someone's B cells.

**Dr. Anastasia Vishnevetsky:** [18:07] And so there's a lot of good data on rituximab there's also additional really good data out of the MS literature about ocrelizumab, not any kind of prospective randomized clinical trials, but large case series and systematic reviews putting together many case series that seem to show that these drugs have been looked at are relatively safe, again except for that, that transient B cell, kind of lowered B cells in the baby. But a really important kind of mindset with this is that it's really a risk benefit. And so, with NMOSD, especially aquaporin-4 positive NMOSD, we know that relapses can be really serious and the name of the game in terms of prevention of disability is prevention of relapses.

**Dr. Anastasia Vishnevetsky:** [19:00] So that's kind of the benefit that we're getting from the therapies. And then I think eculizumab could be a game changer especially if in the future the every eight-week infusion version ends up being approved. Currently eculizumab is every two weeks which is obviously something that you have to consider on top of all of the OBGYN appointments during pregnancy. But I think that's another good option. And we didn't mention specifically satralizumab which is one of the other major drugs used for NMOSD. But satralizumab and it's kind of closely related cousin tocilizumab don't have as much great data in pregnancy. They're in the kind of unknown category but I would probably steer towards one of those B cell depleting therapies like inebilizumab or more specifically rituximab because we have a little more experience or eculizumab during pregnancy.

**Dr. Tamara Bockow Kaplan:** [20:07] Yeah and just to mention with tocilizumab and satralizumab as Anastasia said, we really don't have a lot of great data, but we probably will. Especially there's a lot of post marketing studies and pregnancy registries, you know, with satralizumab and thinking about how women do. But it's always confusing to look at animal data too because for example, in tocilizumab there were some... tocilizumab was associated with fetal toxicity in monkeys, but we haven't seen that in human data. So, it's really hard to extrapolate and we're going to learn more hopefully in the future. And one last point again about eculizumab it was actually also shown to be helpful in a specific syndrome in pregnancy called HELLP syndrome, which is an acronym that stands for something that causes a hypercoagulable state in pregnancy. But essentially it was used to treat pregnant women for a condition that happens in pregnancy. So, I think that's also really reassuring.

**Dr. GG deFiebre:** [21:27] All right, thank you both for that overview. And I think we talked about all the medications including the three that you said were not safe. The only other one Azathioprine. Is there any kind of particular guidance regarding that medication?

**Dr. Anastasia Vishnevetsky:** [21:41] Yes. So, azathioprine does seem to be safe to continue during pregnancy. That being said I think a lot of providers are now steering away from azathioprine just because there are for the most part more effective therapies for the prevention of relapses in seropositive patients. Although there are certainly seronegative patients and or those who have just done well on that medication or prefer an oral option who have been on it for a long time. It doesn't seem to have any increased risk of birth defects from observational studies of women who were exposed during pregnancy. But I think we focused a little bit less on it just because of the efficacy data.

**Dr. GG deFiebre:** [22:29] Got it. Thank you. And so, we talked a little bit about this, but do you mind talking a little bit about how NMOSD is now managed in pregnancy and how this maybe has changed over time?

**Dr. Anastasia Vishnevetsky:** [22:41] Yeah. So, I think there's really been a paradigm shift and we've kind of talked about or alluded to it a few times already where our focus now is really on prevention of relapses and prevention of disease activity and thus prevention of disability accumulation. Whereas in the past, the kind of automatic response we have to pregnancy is always to be very careful and try to avoid medication exposure as much as possible. When we don't know something in pregnancy, we say avoid it. And so that had been the kind of previous guidance and we're luckily, we have enough data now, both in terms of reassuring safety data, but also unfortunately in terms of, you know, just seeing poorer outcomes in patients who aren't treated for a long time. So that's kind of the disease modifying therapy piece and then we'll talk a little bit more about it later on. But in terms of symptomatic medications, we do really still stick to that kind of the paradigm of trying to minimize exposure as much as possible because most of the symptomatic medications that we would use in NMOSD unfortunately just haven't been studied enough to kind of to clearly recommend them.

**Dr. Tamara Bockow Kaplan:** [24:03] And just to add, I think it is really important for your neurologist to have communication with your obstetrician because there's many obstetricians that may not be as familiar with NMOSD and the management of this condition. And there's many neurologists who may not be comfortable managing pregnancy, but hopefully, you know, this can be sort of a multidisciplinary approach to management.

**Dr. Anastasia Vishnevetsky:** [24:33] And kind of on that to emphasize that as well a lot of obstetricians will have a little bit more experience with certain medications during pregnancy and have more comfort with certain medications over others, even beyond kind of like more easily available on Mommy Med or some of the other apps that help you kind of look up drug safety which I would highly recommend by the way. But so, it's very helpful to kind of run different medication options because often stopping all the medications might not be an option. And so, it's a discussion about how to minimize risk and maximize benefits.

**Dr. Tamara Bockow Kaplan:** [25:13] And the last thing to say on that note is it used to be that the FDA had this system of this alphabetical rating system of all these medications that something was labeled A, B, C or X, you know, as a safety in pregnancy. And C meant, you know, we really don't have any data and B was we don't really have that much data and X was an absolutely no. And you know, they've revised that. So, the FDA no longer uses that system and instead write sort of a paragraph about each medication and what we know and what we don't know about its safety use and pregnancy. So, this is... it's a tough conversation and again, you know, I think it's important to weigh the risks and benefits of any medication used during pregnancy for disease management or symptom management.

**Dr. GG deFiebre:** [26:15] Got it. And so, then we've talked about, you know, these medications that their goal is to reduce relapses. But what happens if someone is pregnant and then does have a relapse during pregnancy, how would that be managed?

**Dr. Tamara Bockow Kaplan:** [26:31] Yeah. Sure. So often IV methylprednisolone is used as the first line treatment for relapses and methylprednisolone, prednisone, and prednisolone are preferred in pregnancy because they do not enter fetal circulation as easily. And that's in contrast to dexamethasone where 80% of the maternal dose of dexamethasone can cross the placenta and enter fetal circulation. And you know, if we can avoid fetal exposure to steroids, we hope to. Other studies that are not from the NMOSD population that were much earlier found that there was this correlation in early pregnancy with steroid exposure and the risk of cleft palate in babies. But this really hasn't been confirmed in more recent studies actually that data a lot of it is from use in asthma and inhaled steroids. Which is not at all what we're talking about here and it's unclear if that data holds up. But, if possible, just given this potential theoretical risk. Again, if possible, we aim not to use steroids within that first trimester. Just given any potential risk that there may be. So, there's little data on what to do if IV methylprednisolone fails. We you know typically use plasma exchange or IVIG when we manage NMOSD relapses and in pregnancy we have pretty good data that IVIG is safe and so that is preferred given some potential circulatory risks that may occur with plasma exchange but again there's limited data.

**Dr. Anastasia Vishnevetsky:** [28:22] Talking about IVIG this actually just came up for me for a patient I saw in clinic yesterday with MOG Antibody Disease who was thinking about pregnancy and asking about IVIG. So, we've mostly focused even though we've been using the term NMOSD we're mostly talking about literature that refers to the aquaporin-4 positive population or maybe also the double seronegative population. But for MOG, you know, rituximab is still used somewhat mycophenolate is used but not safe in pregnancy as we talked about. But IVIG is another option that could be very safe during pregnancy and is very effective for the MOG IGG positive patients.



**Dr. GG deFiebre:** [29:14] And just as a follow up question. So, if the aim is to avoid steroid use during the first trimester, if someone has a relapse during the first trimester with the kind of first line treatment for relapse, then it'd be IVIG or is it kind of steroids as well? But managing that kind of risk benefit analysis.

**Dr. Tamara Bockow Kaplan:** [29:35] I think this is really this is where the art and the science merge in the management of NMOSD because there's no right answer. But my personal opinion is I would try IVIG first just given that I know the safety data.

**Dr. GG deFiebre:** [29:56] Got it. Thank you. And so, Anastasia, you mentioned the medications that are used to treat NMOSD symptoms. So, for example, spasticity. So, baclofen would be an example, or medications for pain, or maybe some anticholinergic for example, for bladder issues. Are these safe for pregnant patients or how do you kind of approach this in someone with NMOSD who is pregnant?

**Dr. Anastasia Vishnevetsky:** [30:20] Yeah, it's a challenging question because unfortunately the vast majority of these medications have an unknown or unstudied safety profile in pregnancy. There is a very, very tiny list of patients that are kind of known to be safe. There is a small but somewhat larger risk of medications that are known to be unsafe. And then the vast majority fall into this kind of unknown, some of which are kind of unknown but probably say for unknown but may be safe. Tylenol is the kind of definitely known mainstay for pain and pregnancy that we know is safe. Which is really not super helpful because, you know, if people's pain was easily controlled by Tylenol, they wouldn't be on all these other medications, and they honestly probably wouldn't even be coming in to see us.

**Dr. Anastasia Vishnevetsky:** [31:10] So it feels a little bit, you know, it feels a little bit unsatisfying to say, you know, use Tylenol or use, you know, maybe some meditation or different complementary or alternative therapies to try to manage pain. But that's kind of that's definitely the preferred or kind of more guaranteed safe approach. Then there are some medications to avoid. So definite no no's like carbamazepine or valproic acid. Some patients might be on that for neuropathic pain, although pretty rarely. And then a lot of medications are in the unknown risk or in the unknown risk category. So, baclofen, gabapentin, and tizanidine all fall into that, Botox as well.

**Dr. Anastasia Vishnevetsky:** [31:57] And it would be pretty difficult to find a provider who would provide Botox injections during pregnancy. In all of these situations, there are definitely cases where the benefits of these medications outweigh the risks and patients have to be able to tolerate their day to day lives during pregnancy. And so often there will be an attempt to try to minimize and reduce the doses of these medications as much as possible, leading into pregnancy to see to find kind of the minimal effective dose that works. And then a lot of some of these medications, I'll just mention there are quite a few medications that we use for pain or for mood that are kind of more on the antidepressant category. And there's variable and limited data for safety of many of these medications as well. But if a patient's having suicidal ideations or really severe depression or mood symptoms, it's another situation where the benefits of staying on therapy can outweigh the risks. And actually, another one where interdisciplinary involvement like from a psychiatrist could be helpful as well.

**Dr. GG deFiebre:** [33:16] Thank you. And then Tammy are there any kind of particular... any issues with vaccinations when someone is pregnant with NMOSD or should pregnant patients receive vaccinations?

**Dr. Tamara Bockow Kaplan:** [33:31] The short answer of should patients receive vaccinations is yes, they should. You know we and often times and this is something to talk to your obstetrician about. But often

times in the third trimester women will get a Tdap booster which is the tetanus shot and their flu vaccine. Because we know that provides immunity for your unborn child.

**Dr. GG deFiebre:** [34:03] And then overall in terms of risk factors, Anastasia are those of NMOSD at higher risk for pregnancy loss for fetal abnormalities? And we talked about this a little bit at the beginning.

**Dr. Anastasia Vishnevetsky:** [34:15] So we don't really see higher rates of fetal abnormalities in the babies of patients with NMOSD but as we talked about there are higher rates of miscarriages in particular associated with NMOSD relapse. And that's why we kind of hoped for that year of relative stability prior to conception if possible. And then there are higher rates in the overall NMOSD population of preeclampsia. But when you control for other autoimmune conditions and when you kind of take away the patients who have NMOSD plus other autoimmune conditions, it's less clear whether NMOSD in isolation increases the risk of preeclampsia. So, jury's still out on that one.

**Dr. GG deFiebre:** [35:08] And then Tammy, are there particular issues that might occur during pregnancy and someone with issues like paralysis like bladder issues or increased risk of pressure sores or autonomic dysreflexia?

**Dr. Tamara Bockow Kaplan:** [35:22] This is... it's such a good question and you know, a lot of what we know about this comes from literature of patients with spinal cord injury. So autonomic dysreflexia, you know, headache and nausea are really common during pregnancy, but a pounding headache and nausea can also be a sign of autonomic dysreflexia, and you know, you're sort of at risk for this anytime at least from the spinal cord literature anytime there's an injury at the level of T6 which is your thoracic spine T6 or above. And so, it's important to talk to your obstetrician about this and have a plan and a way to manage it if it does develop. And just to say too that headache is a challenging thing that Anastasia and I deal with a lot as it comes up in pregnancy because people that have headaches or migraines, they may get worse during pregnancy. They may get better, or they may be better and then get worse postpartum because we know that hormones are really affecting our brains, there's some other issues too.

**Dr. Tamara Bockow Kaplan:** [36:38] You know in thinking about someone that may have paraplegia and skin care is really important because pressure ulcers are always a concern but in the setting of pregnancy and weight gain and inability to change position as much and a shift in your center of gravity. It makes that even harder and so again that's something to make sure you're mindful of. And then the two other important issues are urinary symptoms and bowel management. And what makes all of this really complicated is that many of these symptoms are common in NMO and common in pregnancy. And so, so often the question is this NMO or is this pregnancy? Because oftentimes urinary urgency, frequency and even incontinence can happen during pregnancy and also during NMO. But in someone with any sort of paralysis that can be an even bigger issue. And bow management again, constipation is a very common thing in pregnancy. And oftentimes women are told to take iron supplements by their obstetrician which can just compound the problem. So being mindful of this and you know, increasing fluid intake and fruits and vegetables and stool softeners if needed. It's really important to think about.

**Dr. GG deFiebre:** [38:19] And then so if someone has a suspected relapse or is maybe having a relapse and they need to get an MRI is this safe for pregnant patients, Anastasia?

**Dr. Anastasia Vishnevetsky:** [38:29] Yeah. Absolutely. MRIs are definitely safe in pregnant patients and that's... so it's important to kind of draw the distinction between MRIs and CAT scans in that respect. CAT scans we tried very much to avoid in pregnant patients, but MRIs are safe but with a caveat. So, both CAT scans and MRIs use contrast. They use different types of contrast, totally different kind of unrelated substances. So, in



MRI the contrast substance is called gadolinium and gadolinium is not necessarily safe in pregnancy. And we try to avoid gadolinium during pregnancy so you can get an MRI without gadolinium or without contrast, those are kind of synonymous. And you compare that to the preconception MRI if someone has new neurologic symptoms in pregnancy and if there's a new lesion then you can and perhaps it kind of makes sense with the new symptoms then that it will tell you that this is probably a newer active lesion.

**Dr. Anastasia Vishnevetsky:** [39:37] The point of the contrast and why we get MRIs with contrast normally is that it can help us determine if a lesion is active or if there's active inflammation. And there's some data that perhaps gadolinium is safe kind of in that maybe safe, probably safe, unknown kind of category. And so, if there was an absolute emergency where you needed it, that could be a possibility but that really shouldn't come up in in NMOSD as long as there's a good baseline comparator MRI the lack of gadolinium in the MRI is unlikely to change our treatment decisions and we really should be able to get pretty much all the data that we need with a good MRI. But that's something to discuss when you're thinking about getting pregnant and you have NMOSD is just you know, when was the last MRI? Was it, you know within the last several years? We don't get routine annual MRIs necessarily in patients with NMOSD but is there a relatively recent comparative MRI or is you know has it been five or more years since an MRI was obtained?

**Dr. GG deFiebre:** [40:52] And then I'm thinking about the time birth and after birth is a C-section necessary for someone who might have weakness or paralysis from NMOSD?

**Dr. Tamara Bockow Kaplan:** [41:03] So a lot of people might assume that especially someone with a spinal cord injury or even paraplegia should opt for a C-section but that's not necessarily true. And even women who are paraplegic can still have a vaginal delivery and you know so much of that depends on the pregnancy itself. And in terms of delivery, if it is a vaginal delivery this can be assisted with the obstetrician by vacuum or forceps and also you know even if sensation is an issue. Women with paraplegia can learn how to check for labor by feeling their uterus and learning how to time contractions in a different way. So, it may be just a different type of laboring.

**Dr. Anastasia Vishnevetsky:** [41:56] Yeah and to kind of follow up on that in the spinal cord injury literature where often the injuries will be more severe than in NMOSD patients. There's really varying rates of C-sections that have been reported. So, you know, there definitely is an element of choice and kind of that emphasizes just the importance of thinking about that and approaching it together with your anesthesiologist and OBGYN ahead of time, there are some case series that report extremely high rates of C-section mostly elective in the population with spinal cord injuries. And then others that have a pretty high rate of vaginal delivery. So, it's definitely possible and it's just important to be flexible with it.

**Dr. GG deFiebre:** [42:48] And so we did talk about medications during pregnancy, but what medications are safe to take after pregnancy. So, during the breastfeeding period, Tammy?

**Dr. Tamara Bockow Kaplan:** [42:58] Sure. You know, this is an area of even more limited literature but there was a recent publication about looking at rituximab in breast milk and they found that approximately the ratio was about 1-240 of the maternal serum level that was found in the milk. And this led to a less than 1% relative infant dose, which, you know, in the world of safe medications for breastfeeding that's extremely low. We really don't get that concerned unless the relative infant dose is above 10%. And you know, if you think about it, it makes sense to be able to breastfeed with these monoclonal antibodies because it's likely that such a little amount gets into the breast milk at all given the size of these molecules and the molecular weight and then whatever is transferred into the milk is likely destroyed in the baby's gut, in the gastrointestinal track. But we don't have the official data and clearance from the FDA to say this is safe during pregnancy. But what's most important is to think about maternal health. You know there's so much pressure on women

about breastfeeding and women put pressure on themselves. And you know people say breast is best, but the truth is fed is best and you can have a happy, healthy baby that you breastfeed, that you formula feed, that you do a mix of breast and formula. So, a lot of this is a very personal decision and should be discussed with your neurologist and your obstetrician.

**Dr. Anastasia Vishnevetsky:** [44:58] And I do think this data though and more data that hopefully comes out like this will be helpful in facilitating those discussions and allowing women who do want to breastfeed or for whom breastfeeding is a priority to do that while you know also being safe because that postpartum period again is that highest risk period and preventing maternal disability is so important. Both, you know, most importantly for mom but also for baby's long-term health and long-term outcomes. So, you know it's really encouraging to start seeing some of this data about safety in breastfeeding.

**Dr. GG deFiebre:** [45:45] Alright well thank you both so much. Are there any kind of final thoughts or last thoughts you want to add? We've covered a lot with some really great information.

**Dr. Tamara Bockow Kaplan:** [45:56] I guess. I just want to reiterate that pregnancy is possible with NMOSD, and it can be a beautiful healthy happy pregnancy. And it just you know it takes planning and it takes coordination with your neurologist and your obstetrician and making sure everyone is aware of your wishes and your plans and coming up with a care plan.

**Dr. Anastasia Vishnevetsky:** [46:26] And then also that there's a lot of encouraging new work in this and we hopefully will have more data about safety in pregnancy in breastfeeding in the next several years. The drugs we're using are still pretty new and so we're still waiting on that.

**Dr. GG deFiebre:** [46:41] Great, well thank you both so much. We really appreciate it.

**Dr. Anastasia Vishnevetsky:** [46:44] Thank you.

**Dr. Tamara Bockow Kaplan:** [46:44] Thank you.